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MECANISMOS DE CODIFICACIÓN Y PROCESAMIENTO DE INFORMACIÓN EN REDES BASADAS EN FIRMAS NEURONALES

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A mi familia

Lo importante en la ciencia no es tanto obtener nuevos datos,
sino descubrir nuevas formas de pensar sobre ellos.

William Lawrence Bragg

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Abstract

Neural signatures are very robust and precise temporal structures that have been described within the bursts of activity of distinct families of biological neurons. They receive their name from the fact that they are characteristic of each neuron in the network, so that they would allow the identification of the origin of neural signal. In some cases, such as the CPG (Central Pattern Generator) pyloric of crustaceans, it has been demonstrated that the signature of their neurons is robust even between individuals of distinct species. The existence of such structures and their conservation in evolution raises many interesting questions for the scientific community. However, today, although its existence is known for different families of neurons, both invertebrates and vertebrates, it is not known whether these very precise temporal structures and characteristics may have some functional significance for the circuits at which they are present. Only a few computational works with CPG circuit models seem to indicate that information processing based on the identification of the origin of neural signals could be a plausible and highly efficient strategy for the nervous system. This doctoral thesis extends previous computational studies with new models and experiments that allow the study of collective dynamics and emerging properties of systems formed by neurons with the ability to recognize and emit characteristic neural signatures.

The proposed network models show a great dynamic richness in response to stimuli introduced in few neurons of the network, being able to store simultaneously multiple neuronal signatures by means of coexistent space-temporal patterns that propagate through the network. Among these patterns it is established a winnerless or winner take all competition dynamics as a function (i) intra-unit parameters associated with the recognition and emission of signatures; and (ii) the network topology. In addition, models consisting of neurons with the ability to encode information in additional dimensions show that the same network could simultaneously process information encoded in different aspects of its input signals. In particular, in our experiments we study the dynamics of networks capable of encoding information in two simultaneous and independent modalities: one based on the recognition and emission of neural signatures; and the other based on the encoding of information at the firing frequency of the neurons in the network. The combination of multiple simultaneous coding schemes allows the network to generate coexisting patterns of activity coding the information in different dimensions. In this way, we have developed models capable of storing in their collective dynamics the information of distinct rhythms (frequency) received as an external stimulus, as well as which have been the stimulated neurons of the network (identified through their signature). For each dimension, we observe different collective dynamics and complex self-organizing properties

Finally, we have used a conductance-based neuron model to study its ability to detect specific activation sequences by recognizing specific neural signatures that identify the different emitters of their input signals. The neuron receives a coordinated combination of signed signals and we study its response to different combinations. Simulations indicate that the reading neuron could use the signatures to contextualize the incoming signals and, consequently, calculate a characteristic response based on the precise phase relationships between the activity of different emitters.

The results obtained in this thesis indicate that information processing based on the identification of neural signals could be a powerful coding and processing strategy for neural systems. In addition, we argue that plasticity mechanisms within individual cells and multicode coding strategies (based on multiplexing different types of information in the same signal) can provide additional computational properties to neural networks, which could improve their capacity and performance in a wide variety of tasks. For example, such mechanisms would provide individual neurons with improved capabilities to control and negotiate coordinated sequential dynamics.

Resumen

Las *firmas neuronales* son unas estructuras temporales muy robustas y precisas que se han descrito dentro de las ráfagas de actividad de distintas familias de neuronas biológicas. Reciben su nombre del hecho que son características de cada neurona de la red, de manera que permitirían identificar el origen de una señal neuronal. En algunos casos, como en el del CPG (Generador Central de Patrones) pilórico de los crustáceos, se ha demostrado que la firma de sus neuronas es robusta incluso entre individuos de distintas especies. La existencia de este tipo de estructuras y su conservación en la evolución plantea múltiples cuestiones interesantes para la comunidad científica. Sin embargo, a día de hoy, aunque se conoce su existencia para distintas familias de neuronas, tanto de invertebrados como de vertebrados, se desconoce si estas estructuras temporales tan precisas y características pueden tener algún significado funcional para los circuitos en los que aparecen. Solo algunos trabajos computacionales con modelos de circuitos generadores centrales de patrones parecen indicar que el procesamiento de información basado en la identificación del origen de las señales neuronales podría ser una estrategia plausible y altamente eficiente para el sistema nervioso. Esta tesis doctoral amplia los estudios computacionales previos, con nuevos modelos y experimentos que permiten estudiar la dinámica colectiva y las propiedades emergentes de sistemas formados por neuronas con la capacidad de reconocer y emitir firmas neuronales características.

Los modelos de red propuestos muestran una gran riqueza dinámica en respuesta a estímulos introducidos en pocas neuronas de la red, siendo capaces de almacenar simultáneamente múltiples firmas neuronales mediante patrones espacio-temporales coexistentes que se propagan por la red. Entre estos patrones se establecen dinámicas de competición con o sin ganador, temporales o permanentes, en función (i) de los parámetros intra-unidad asociados al reconocimiento y emisión de las firmas; y (ii) de la topología de la red. Adicionalmente, los modelos constituidos por neuronas con capacidad de codificar información en dimensiones adicionales, muestran que una misma red podría procesar simultáneamente información codificada en distintos aspectos de sus señales de entrada. En particular, en nuestros experimentos estudiamos la dinámica de redes capaces de codificar información en dos modalidades simultáneas e independientes: una basada en el reconocimiento y emisión de firmas neuronales; y otra basada en la codificación de información en la frecuencia de disparo de las neuronas de la red. La combinación de múltiples esquemas de codificación simultáneos permite a la red generar patrones coexistentes de actividad codificando la información en diferentes dimensiones. De esta forma, hemos desarrollado modelos capaces de almacenar en su dinámica colectiva la información de distintos ritmos (frecuencia) recibidos como estímulo externo, así como cuáles han sido las neuronas de la red estimuladas (identificadas a través de su firma). Para cada dimensión, observamos diferentes dinámicas colectivas y propiedades auto-organizativas complejas.

Por último, hemos utilizado un modelo de neurona basado en conductancias para estudiar su capacidad para detectar secuencias de activación específicas por medio del reconocimiento de firmas neuronales específicas que identifican a los distintos emisores de sus señales de entrada. La neurona recibe una combinación coordinada de señales firmadas y estudiamos su

respuesta a distintas combinaciones. Las simulaciones indican que la neurona lectora podría usar las firmas para contextualizar las señales entrantes y, en consecuencia, calcular una respuesta característica en función de las relaciones de fase precisas entre la actividad de distintos emisores.

Los resultados obtenidos en esta tesis indican que el tratamiento de información basada en la identificación de las señales neuronales podría ser una potente estrategia de codificación y procesamiento para los sistemas neuronales. Además, argumentamos que los mecanismos de plasticidad dentro de las células individuales y las estrategias de codificación multicódigo (basadas en la multiplexación de distinto tipo de información en una misma señal) pueden proporcionar propiedades computacionales adicionales a las redes neuronales, lo que podría mejorar su capacidad y rendimiento en una amplia variedad de tareas. Por ejemplo, disponer de este tipo de mecanismos proporcionaría a las neuronas individuales capacidades mejoradas para controlar y negociar dinámicas secuenciales coordinadas.

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--- INTRODUCCIÓN GENERAL ---

El trabajo de investigación presentado en esta memoria de tesis doctoral está enmarcado en el contexto de la neurociencia computacional y de la neuroinformática. Ambos campos estudian el sistema nervioso desde distintas perpectivas, principalmente en las tareas relacionadas con la codificación y procesamiento de información. La neurociencia computacional es un campo maduro de investigación al día de hoy, que combina el análisis matemático y las simulaciones por computadora para estudiar y predecir el comportamiento del sistema nervioso (Stern and Travis, 2006). Busca entender cuáles son los mecanismos (los procesos, los "algoritmos") mediante los cuales el sistema nervioso analiza la información para cumplir su objetivo. Es un campo interdisciplinario para el desarrollo, simulación y análisis de modelos multiescala que permitan formular hipótesis de la función neuronal que pueden ser verificadas en experimentos biológicos (Yarom, 1991; LeMasson *et al.*, 1995; Pinto *et al.*, 2000; Szücs *et al.*, 2000; LeMasson *et al.*, 2002; Olypher *et al.*, 2006). Para una mejor comprensión del sistema nervioso, se basa en datos experimentales y modelos teóricos desde el nivel de moléculas, a través de células y redes, hasta la cognición y el comportamiento. Estos modelos capturan las características esenciales de los sistemas biológicos con distinto nivel de detalle y a escalas espacio-temporales múltiples (Torres and Varona, 2012). El modelado podría darnos una idea de los posibles mecanismos de codificación y procesamiento de información subyacentes, en los elementos individuales y en los elementos organizados colectivamente, que conforman el sistema nervioso.

La neuroinformática combina la neurociencia y las ciencias de la información, mediante la aplicación de modelos computacionales y herramientas informáticas analíticas, para una mayor comprensión de la funcionalidad del sistema nervioso (Linne, 2018) y del cerebro (Dashti *et al.*, 1997; Eckersley *et al.*, 2003; Pittendrigh and Jacobs, 2003; Rueden *et al.*, 2004; van Pelt *et al.*, 2001). Este campo se ocupa del intercambio, integración y análisis de grandes volúmenes de datos heterogéneos y complejos, recopilados en múltiples niveles de investigación, a través del desarrollo de diferentes sistemas de datos que pueden funcionar juntos, convirtiéndose en interoperables (ver informe sobre neuroinformática del grupo de trabajo sobre neuroinformática del foro mundial de ciencias de la OCDE, 1999, 2002, y publicaciones impresas del grupo de neuroinformática, (Amari *et al.*, 2002; Eckersley *et al.*, 2003; Nayak *et al.*, 2018; Wróbel, 2005)). Esto la convierte en una interfaz entre la informática y la neurociencia experimental.

El Sistema Nervioso

En las últimas décadas, el avance en el estudio del sistema nervioso ha proporcionado una gran cantidad de nuevos datos que han contribuido y resultan de gran interés para la comunidad científica en general y, en particular, para el campo de la neurocomputación y de la neuroinformática, para comprender los mecanismos que subyacen al funcionamiento del sistema nervioso. El sistema nervioso es el encargado de llevar a cabo la mayoría de las funciones de control y coordinación de actividades en los metazoos superiores. Por un lado, en su nivel de actuación más simple, regula el medio interno controlando respuestas autónomas y endocrinas. Por otro lado, en un nivel más complejo, es

el responsable de realizar la comunicación con el medio externo, a través de las funciones sensoriales y motoras (Negru, 2016). Esto posibilita una interacción con el medio de una manera eficaz, correcta y oportuna.

En general, el sistema nervioso capta y procesa información (estímulos), y genera la respuesta. Siguiendo este flujo de información neuronal, provocado por distintos estímulos, podemos considerar que el sistema nervioso está conformado por tres subsistemas fundamentales: sistema sensorial, sistema central y sistema motor, los cuales se encargan básicamente de:

- Detectar lo que sucede en el interior del cuerpo y en el mundo que nos rodea (sistema sensorial: estímulos),
- Procesar esta información e integrarla con la actividad interna del sistema nervioso, y si es posible, relacionarla con la experiencia (sistema central: procesamiento),
- Almacenar esta información (sistema central: almacenamiento), y/o
- Producir una respuesta, la más adecuada posible, para acomodarse a la nueva situación o quizás alterarla (sistema motor: comportamiento).

Como consecuencia de la llegada de estímulos típicamente se pueden producir respuestas de dos tipos: movimientos y secreciones. Los movimientos, realizados por los órganos efectores, son respuestas rápidas, puntuales y de duración breve. En cambio, las secreciones, realizadas por las glándulas del sistema endocrino, son lentas, sostenidas y duraderas.

La estructura del sistema nervioso, es muy compleja y dependiente del organismo o sistema objeto de estudio, está constituido por células especializadas (las neuronas), que se conectan unas con otras (la sinapsis), formando las denominadas redes neuronales que se organizan de acuerdo a un patrón de conexión, y que permiten que el sistema cumpla de manera eficiente e integrada, su función. En las siguientes secciones se describe con un poco más en detalle la estructura del sistema nervioso.

Por otro lado, el sistema nervioso es capaz de realizar una gran cantidad de tareas de manera rápida y eficiente bajo diversas condiciones de error, en forma paralela. La información se procesa simultáneamente en diferentes regiones que se coordinan para realizar una tarea específica. Estas tareas se aprenden y perfeccionan a lo largo del tiempo con la experiencia. Por ello, el sistema nervioso es un buen modelo a imitar ya que tiene una gran cantidad de información y muchas características que son importantes e interesantes de reproducir en muchos sistemas artificiales, en diversos campos de la ciencia. La neurocomputación intenta proporcionar a los sistemas artificiales alguna de las habilidades mencionadas anteriormente inspirándose en la forma en que los sistemas biológicos procesan la información (Fausett, 1994; Haykin, 1998). Es decir, toma inspiración en el sistema nervioso y trata de explicar este comportamiento a través de modelos.

NEURONAS

El sistema nervioso está formado por neuronas (Ramón y Cajal, 1892; Ramón y Cajal, 1894; Ramón y Cajal, 1909; Ramón y Cajal, 1911), que son células con un alto grado de especialización, consideradas como unidades básicas de procesamiento y transmisión de información neuronal (Kandel *et al.*, 1991). Las neuronas integran la respuesta de un organismo a estímulos, a través de impulsos electroquímicos (información), que viajan desde

una neurona origen (neurona presináptica) hasta la célula objetivo (neurona postsináptica).

Una neurona posee, como cualquier otra célula, una membrana citoplasmática, un citoplasma y un núcleo. La membrana es la frontera entre el interior y el exterior de la célula, separando el citoplasma del medio externo. En el caso de las neuronas, esta función juega un papel fundamental en la recepción y transmisión de impulsos electroquímicos. El citoplasma es la parte de la célula que rodea al núcleo y está envuelto por la membrana citoplasmática. El núcleo se encuentra situado en el cuerpo celular y se encarga de producir energía para el funcionamiento de la neurona.

En general, la neurona se compone por tres partes funcionales: el soma, el axón y las dendritas (Aizawa, 1994). Al cuerpo de la neurona se le conoce como soma y se encarga de ordenar y coordinar todas las funciones de la célula. Las dendritas son prolongaciones cortas y numerosas, que parten del soma, y por lo general, reciben o captan impulsos que proceden de receptores sensoriales o de otras neuronas (Herreras, 1990; Chen *et al.*, 1997; Stuart *et al.*, 1997). El axón es una prolongación generalmente única y larga que actúa como conductor de señales de salida a otras neuronas o a los órganos efectores. El axón tiene una doble misión, por una parte, une a las neuronas entre sí (sinapsis) y, por otra, al reunirse con cientos o miles de axones, da origen a los nervios que conectan al sistema nervioso con el resto del cuerpo. En la figura 1 se representa el esquema de una neurona con sus componentes principales.

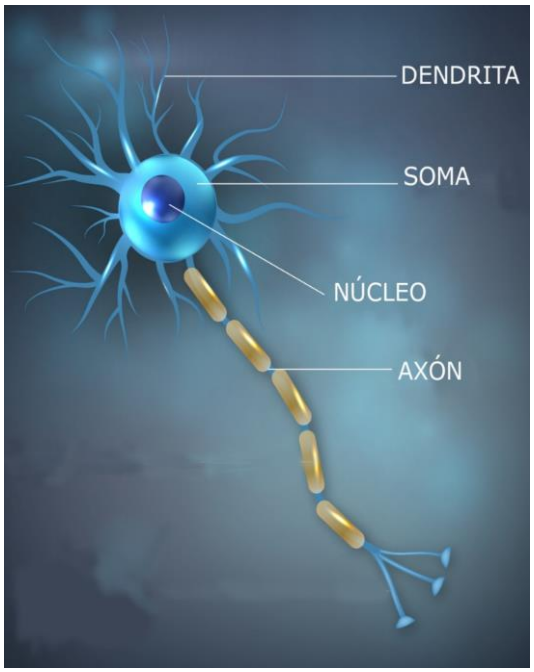

Figura 1. Diagrama básico de una neurona genérica. Las funciones más básicas de las neuronas son recibir información y transmitirla a través de impulsos electroquímicos a lo largo de grandes redes de comunicación por todo el sistema nervioso. Imagen tomada y modificada de https://www.freepik.es/vectorratis/ilustracion-partes-neurona_837995.html

Existen diferentes tipos de neuronas, pero dependiendo de su funcionalidad pueden clasificarse en: neuronas sensoriales, interneuronas y motoneuronas. Las neuronas sensoriales son las encargadas de recabar información procedente de los estímulos, relacionada con lo que está sucediendo dentro y fuera del cuerpo y transformar dicha información en impulsos electroquímicos. Las interneuronas, o neuronas integradoras procesan la información de forma local, para luego transmitirla codificada en impulsos eléctricos, hacia otra célula, a través de las vías nerviosas. Las motoneuronas reciben la información de las neuronas sensoriales o de las interneuronas e inervan de forma directa a los órganos efectores (músculos).

SINAPSIS

Las neuronas se comunican unas con otras mediante conexiones, conocidas como sinapsis. Las sinapsis pueden ser eléctricas o químicas. Una única neurona puede resultar afectada simultáneamente por múltiples sinapsis, con muchos axones de diferentes neuronas (Yuste and Majewska, 2001).

SINAPSIS ELÉCTRICAS

En las sinapsis eléctricas existe una conexión muy cercana entre la neurona presináptica y la neurona postsináptica, con una separación entre sus membranas de unos pocos nanómetros (Connors and Long, 2004). La trasmisión del impulso eléctrico se realiza de forma directa al fluir los iones de una neurona a otra (Bear *et al.*, 1996), de una manera muy rápida y casi inmediata. Las conexiones eléctricas, en su gran mayoría, fluyen en ambas direcciones y con la misma intensidad ("gap juctions") (Galarreta and Hestrin, 2001). Dada la forma en que se producen este tipo de sinapsis no permite que una neurona inhiba la actividad de otra. Las sinapsis eléctricas son mucho más rápidas, y apenas sin retardos, en comparación con la sinapsis química (Kandel *et al.*, 1991; Paniagua *et al.*, 1998).

SINAPSIS QUÍMICA

En este tipo de sinapsis, la separación entre neuronas es mayor que en las sinapsis eléctricas, alrededor de 20-40 nm, por lo que no hay contacto físico entre neuronas (Cowen et al., 2001). Para establecer la conexión es necesario que la neurona presináptica libere ciertas sustancias químicas denominadas neurotransmisores. Cuando estas sustancias llegan a la membrana de la neurona postsináptica, atravesando la hendidura sináptica (pequeño espacio que sirve de vía para la transmisión de la información), provocan ciertos cambios químicos en su configuración, que permiten el intercambio de determinados iones entre el medio extra e intracelular, lo que hace que el impulso nervioso se propague (Gómez, 2011). El transporte de la señal es en una dirección, es decir, la información fluye desde la neurona presináptica hacia la neurona postsináptica (Margeta and Shen, 2010). En este tipo de sinapsis algunas neuronas pueden potenciar y/o inhibir la actividad de otras.

POTENCIALES DE ACCIÓN

En el borde de la membrana neuronal existe una diferencia eléctrica (voltaje), con cargas (iones) positivas afuera y negativas adentro, llamada potencial de membrana. Con el movimiento de las moléculas a través de los canales iónicos el potencial de membrana varía y estas variaciones son las que definen el comportamiento de las neuronas. La evolución temporal del potencial de membrana permite caracterizar este comportamiento. El potencial de membrana cuando la neurona no recibe ningún tipo de estímulo se conoce como potencial de reposo, que se caracteriza por un valor entre -60 y -70 milivoltios (mV) (Kandel *et al.*, 1991), por lo que, el interior de la célula está cargada negativamente en relación con su exterior.

Una fluctuación rápida del potencial de membrana que alcanza un valor pico de voltaje para posteriormente disminuir su valor hasta alcanzar el potencial de reposo en un corto período de tiempo (1 ms) se conoce como potencial de acción (spike en inglés). Es decir, son impulsos rápidos y transitorios que siguen la ley del todo o nada. La recepción de un potencial de acción presináptico en una neurona puede provocar cambios en el potencial de membrana que significarían la generación de nuevos potenciales de acción y por consiguiente su propagación. Estas alteraciones pueden ser excitatorias (lo que facilita la generación de un potencial de acción) causando una despolarización, o ser inhibitorias (lo que dificulta la aparición de un potencial de acción) causando una hiperpolarización, que puede terminar o

no con la generación de un nuevo potencial de acción, por parte de la neurona postsináptica (Wilkens, 2008). La despolarización es el proceso que hace que el potencial en el interior de la célula se vuelva más positivo que el nivel del potencial de reposo. La hiperpolarización, en cambio, es el proceso que hace que el potencial en el interior de la célula se vuelva más negativo que el nivel de potencial de reposo. Si la despolarización alcanza un umbral se genera un potencial de acción, caso contrario no, ver figura 2.

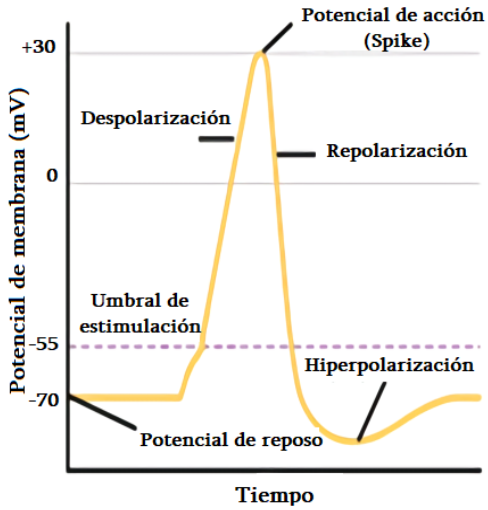

Figura 2. Representación de un potencial de acción o spike. Cuando el potencial de membrana supera un valor umbral, comienza una fase de despolarización hasta alcanzar un valor pico a partir del cual disminuye su valor, entrando en la fase de repolarización, disminuyendo aún más hasta llegar a la fase de hiperpolarización para al final alcanzar la zona de reposo. Imagen modificada de "Cómo se comunican las neuronas: figura 3", de OpenStax College, Biología (CC BY 3.0), https://es.khanacademy.org/science/biology/human-biology/neuron-nervous-system/a/depolarization -hyperpolarization-and-action-potentials, revisada el 14 de mayo de 2019.

Una vez producido un potencial de acción, casi instantáneamente, se produce una hiperpolarización (Gerstner *et al.*, 2014; Purves, 2004). En este estado la neurona está inhibida, es decir, será imposible desencadenar un segundo potencial de acción durante un cierto intervalo de tiempo, denominado período de refracción. Este período es independiente de la intensidad del estímulo que llega a la neurona.

La generación de potenciales de acción permite a las neuronas interactuar entre sí. Los potenciales de acción son los encargados de codificar la información que se propaga por el sistema nervioso tanto en una escala espacial como temporal (Krebs, 2011; Bialek et al., 1991; Kandel et al., 1991; Rieke et al., 1999).

COMPORTAMIENTO EN RÁFAGAS

Cuando los potenciales de acción se generan de forma aislada, se dice que la neurona tiene comportamiento spiking (ver panel A, figura 3). Sin embargo, en muchas ocasiones la generación de potenciales de acción no se produce de forma aislada. Cuando el comportamiento se caracteriza por la generación de un grupo de potenciales de acción, en un corto intervalo de tiempo, alternándose con períodos de silencio (en donde, únicamente se presenta actividad subumbral), a esta agrupación se le conoce como ráfagas (o burst en inglés). Las neuronas con actividad en ráfagas o bursting presentan un comportamiento que se caracteriza por la alternancia de periodos de gran actividad con fases en las que la neurona

está en reposo (ver panel B, figura 3).

La actividad bursting es mucho más rica que la actividad spiking, desde el punto de vista de la combinación de diferentes escalas temporales, y está presente en muchas células de diferentes sistemas nerviosos (Gola and Selverston, 1981; Hu and Bourque, 1992; Smith *et al.*, 1975; Sugaya and Onozuka, 1978). Dependiendo del sistema y del estado de procesamiento de la neurona puede presentar comportamientos regulares, irregulares o caóticos. Cabe notar que, en ausencia de estímulos toda neurona genera una actividad espontánea.

En la visión tradicional, las ráfagas son consideradas como elementos unitarios que contienen información redundante y que los potenciales de acción se agrupan como mecanismos de seguridad ante posibles errores, es decir, si un spike se pierde, muy cerca en el tiempo, llega otro spike que contene la misma información (Lisman, 1997). En la visión actual, existen muchos trabajos, que consideran a las ráfagas como unidades que pueden tener información por sí mismas o incluso en la codificación una mayor cantidad de información que el propio potencial de acción , debido a la existencia de distintas escalas temporales en las que se puede codificar (Reinagel *et al.*, 1999).

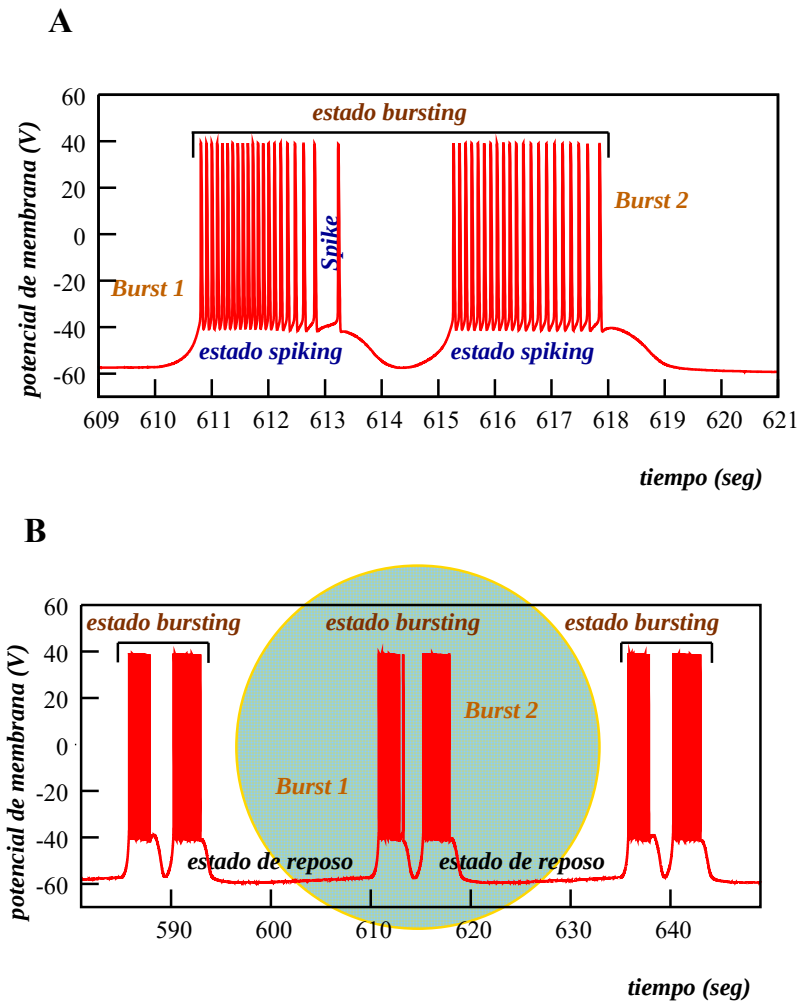

Figura 3. Ejemplo del comportamiento spiking-bursting de una neurona. El panel A es un acercamiento de una de las secuencias de actividad (delimitada en el panel B por el círculo de color verde). Cada burst contiene una agrupación de potenciales de acción o spikes separados por un período de relajación. En el panel B se observan tres secuencias de actividad spiking-bursting, separados por estados de reposo. En este caso, una secuencia contiene un par de bursts.

En los últimos años se ha prestado mayor atención al rol que puede desempeñar la actividad "spiking" en sistemas con comportamiento bursting. Desde el punto de vista de codificación y procesamiento de información, la actividad spiking-bursting es uno de los comportamientos más interesantes que puede presentar una neurona. Esta es una estrategia efectiva en la codificación de distintos tipos de información, al combinar al menos dos tipos de actividad para codificar respuestas a diferentes estímulos sensoriales (Izhikevich, 2006). En función de la entrada sensorial se pueden producir distintas respuestas (Gabbiani *et al.*, 1996, Doiron *et al.*, 2003; Oswald *et al.*, 2004), de acuerdo al tipo de procesamiento en las diferentes escalas temporales (Buzsaki, 2006). En este contexto vamos a estudiar el rol que juegan los distintos mecanismos de codificación y procesamiento de información neuronal, basados en diferentes escalas temporales, para producir distintas respuestas sensoriales.

MECANISMOS DE CODIFICACIÓN Y PROCESAMIENTO DE INFORMACIÓN

Una de las funciones, quizás la más importante, del sistema nervioso es el procesamiento de información. Las neuronas se conectan entre sí para formar elementos de procesamiento de nivel superior (circuitos o redes neuronales) y se comunican con órganos sensoriales y/o efectores (los músculos) para dar una respuesta adecuada ante un estímulo y realizar tareas complejas. El procesamiento no es un proceso pasivo de entrega de mensajes cerrados, en cada paso se realiza un análisis del mensaje, y se completa con precisión sus contenidos. No obstante, antes de procesar la información sensorial, el sistema nervioso procede a depurar la información; siendo esto, una primera selección. Una reacción sensitiva produce, en muchas ocasiones, una reacción inmediata del sistema nervioso o en otros casos la formación del recuerdo de la experiencia, pudiendo ser conservada minutos, días o años.

El procesamiento de información en el sistema nervioso se realiza de forma rápida y eficiente. Para ello, se utiliza un conjunto de códigos propios mediante los cuales se representan los estímulos que se reciben del exterior. Las neuronas se envían información de unas a otras utilizando estos códigos, optimizando las capacidades de memoria y aprendizaje (Stevens and Zador, 1995; Ferster and Spruston, 1995; Gerstner *et al.*, 1997; Nádasdy, 2000). En la gran mayoría de sistemas neuronales se puede asumir que los códigos neuronales se basan en la generación de potenciales de acción o spikes, sin embargo, aún no está clara la forma exacta de cómo se codifica y procesa la información. Habitualmente, se describen mecanismos de codificación basados en codificación espacial o en codificación temporal de información o en una combinación de ambas (codificación espacio-temporal). En estos tipos de codificación, en ocasiones, no se puede hacer una distinción clara entre ellos, ya que están muy relacionados (Theunissen and Miller, 1995). En una codificación espacial lo que importa es la densidad de potenciales de acción (número de potenciales de acción). En cambio, en una codificación temporal se asume que lo que importa es la secuencia específica de potenciales de acción, su relación en el tiempo (tiempos precisos en la generación de potenciales de acción) y no sólo su densidad. Esto ha hecho que exista una mayor relevencia en la codificación temporal (Bialek et al., 1991; Softky, 1995; Rieke *et al.*, 1997; de Ruyter van Steveninck *et al.*, 1997; Berry *et al.*, 1997; Buracas *et al.*, 1998). En esta tesis se van a estudiar posibles mecanismos de codificación y procesamiento de información basados en la codificación de los potenciales de acción.

Estudio del Sistema Nervioso: Modelos

Para modelar el comportamiento de los componentes del sistema nervioso, se suelen seguir dos estrategias: el enfoque botton-up, permite desarrollar modelos biofísicos detallados a partir de los datos obtenidos en estudios experimentales y el enfoque top-down, que pretende capturar características esenciales de los sistemas biológicos con distinto nivel de detalle y encontrar mecanismos generales que los causan, mediante paradigmas simplificados. Ambos tipos de modelos permiten proponer nuevas hipótesis y sugerir experimentos, que pueden ser verificados y/o validados en el laboratorio, estos dos enfoques pueden combinarse.

En el sistema nervioso el comportamiento exhibido por las redes neuronales, en todas las ocasiones, es consecuencia de la dinámica colectiva de red. En nuestro caso, utilizamos el enfoque top-down, porque estamos interesados en construir una red neuronal modelada por el comportamiento individual de una neurona (modelo de neurona) y por la forma en la cual estas se conectan entre sí (modelo de sinapsis), para analizar la dinámica colectiva y la influencia de los patrones de conectividad en las propiedades emergentes de la red. Los tipos de modelos de red neuronal que se estudiarán en este trabajo de investigación son redes neuronales capaces de procesar y reconocer códigos neuronales, en donde, el comportamiento de las neuronas se caracteriza por la generación de ráfagas (burst) de potenciales de acción (spikes).

MODELOS DE NEURONA

Los modelos de neuronas son la base para construir y estudiar variadas redes bio-inspiradas, y así comprender, simular y reproducir un determinado comportamiento neuronal. Dependiendo del nivel de detalle se puede simular a niveles inferiores (celulares y/o moleculares) y superiores (aspectos funcionales). Se pueden aplicar modelos, que no simulan ningún parámetro real, pero toman en cuenta aspectos cualitativos del comportamiento neuronal. En las últimas décadas se han propuesto modelos con varias descripciones matemáticas, que simulan características más realistas (Koch, 1999; Torres y Varona, 2012), desde modelos de integración y disparo hasta modelos de tipo Hodgkin-Huxley (ver sección: modelos biofísicos). Lo que hace de estos modelos, herramientas fundamentales para comprender el sistema nervioso.

Dependiendo del tamaño de la red y del fenómeno objeto de estudio, los modelos a menor escala pueden ser los más adecuados por su sencillez, aunque sean poco realistas. Sin embargo, cuando se quiere obtener más realismo, los modelos son más complicados y más difíciles de analizar, debido al gran número de parámetros que tienen. Nuestro interés se centra en el procesamiento de información neuronal, en neuronas individuales y en redes de neuronas, fáciles de entender, modelar y simular (Torres and Varona, 2012). Su principal elemento son los potenciales de acción.

Modelos Biofísicos

Los modelos biofísicos permiten describir la generación de potenciales de acción en términos de las propiedades eléctricas de las membranas citoplasmáticas. Este tipo de modelos permiten

simular la actividad neuronal mediante ecuaciones diferenciales no lineales. Estos modelos pueden reproducir la dinámica rica y compleja de neuronas reales, integrando, con bastante precisión, cada uno de los comportamientos de las neuronas, que forman parte de una red neuronal.

En 1952, Hodgkin y Huxley establecieron un modelo fisiológico realista experimental sobre la dependencia del voltaje de conductancia de iones, en la membrana eléctricamente excitable del axón gigante de calamar (Hodgkin and Huxley, 1952; Koch, 1999). Es un modelo clásico para simular el comportamiento de las neuronas que permite describir sus propiedades eléctricas activas (dependientes del voltaje) y pasivas (capacitivas e independientes del voltaje). Este modelo es la representación matemática mediante el cual se estudia el comportamiento de la transmisión del potencial de acción a lo largo de una neurona. El modelo se basa en cuatro dimensiones con variables de estado, como el voltaje que viaja a través de la membrana y la probabilidad de que se abran los canales de sodio y de potasio, el primer canal se encarga de despolarizar la membrana, en cambio, el segundo canal se encarga de hiperpolarizar la membrana de la neurona. Este modelo es el más importante en neurociencia computacional, por cuanto, es la base matemática de modelos realistas actuales, conocidos como modelos simplificados. Estos tratan de reducir la complejidad del modelo Hodgkin y Huxley, mediante un número reducido de variables (y/o la no linealidad asociada), para recrear una serie de características de la neurona y así reducir los cálculos computacionales para ser analizados matemáticamente. Las simulaciones con grandes redes permiten capturar la esencia del comportamiento neuronal. Desde el punto de vista del sistema dinámico, describe fenómenos emergentes de la red debido a la sincronización de muchas unidades. Para ello, puede ser suficiente utilizar un modelo simplificado y reproducir características fundamentales de la actividad neuronal. Algunos de estos modelos simplificados que podemos mencionar: el modelo de Fitzhugh-Nagamo, el de Morris-Lecar, el de Hindmarsh–Rose, el de Integración y Disparo, o el de McCulloch and Pitts, entre otros. Uno de los modelos que se utiliza en este trabajo es el modelo de Komandantov-Kononenko, que permite reproducir de forma exacta los potenciales de acción (Varona, 1997) y presenta un comportamiento spiking-bursting similar al de circuitos neuronales reales. (Elson *et al.*, 1998; Pinto *et al.*, 2000; Varona *et al.*, 2001), (ver Sección “Procedimientos” – Capítulo 3).

MODELOS DE SINAPSIS

Existen diferentes modelos de sinapsis que toman en cuenta los procesos biológicos que ocurren de forma local en el espacio sináptico entre dos potenciales de acción consecutivos. Estos modelos describen el comportamiento de sinapsis inhibidoras y excitatorias que llegan a una neurona. En los modelos, estas conexiones entre células se representan mediante ecuaciones matemáticas que determinan la cantidad de corriente que fluye entre la neurona presináptica y la postsináptica. La corriente sináptica total que recibe una neurona postsináptica es la suma de la corriente aportada por cada una de las conexiones que establece con otras neuronas. Uno de los modelos de sinapsis que utilizamos en este trabajo de investigación es el modelo de Detehxe (Destexhe *et al.*, 1994), (ver Sección “Procedimientos” – Capítulo 3).

Sistema Nervioso Motor: Movimientos Rítmicos

Los movimientos que realizan los animales son regulados y coordinados por el sistema nervioso motor, a través de músculos, articulaciones y/o huesos. Los cuales permiten moverse y relacionarse con el medio externo, en respuesta a estímulos recibidos. Los movimientos pueden ser de dos tipos: voluntarios e involuntarios (reflejos). Los reflejos son patrones coordinados e involuntarios de contracción y relajación muscular desencadenados por estímulos periféricos. Estos producen respuestas rápidas estereotipadas e involuntarias. Los cuales pueden ser regulados por algunas características del estímulo, por ejemplo, la intensidad. Los movimientos voluntarios son organizados en torno a una acción con un objetivo. Se caracterizan porque son dirigidos y en gran medida aprendidos, como peinarse, lavarse, guiar un vehículo, tocar un instrumento o coger una botella.

Una característica importante que presentan los sistemas motores es la capacidad para adaptarse a los cambios del entorno, para la realización de movimientos precisos (Tseng *et al.*, 2007). Según Grillner and Jessell (2009) la más simple de las tareas motrices, en el más primitivo de los animales, demanda la integración de actividades de circuitos neuronales. Muchos movimientos como respirar, masticar, caminar, volar, nadar, son sólo algunos ejemplos que implican una activación rítmica, es decir, secuencias de actividad que se repiten en el tiempo. Lo que hace que el sistema nervioso produzca patrones espacio-temporales estereotipados de contracción muscular, que pueden estar presentes en diversos grupos de músculos. A estos movimientos musculares se les denominan "patrones motrices", y como podemos darnos cuenta resultan fundamentales para la vida animal.

Generador Central de Patrones

Todos los animales vertebrados e invertebrados realizan movimientos rítmicos que son controlados por los generadores centrales de patrones (CPGs por sus siglas en inglés) (Selverston *et al.*, 2000), de forma que cada individuo/especie está dotado con un amplio repertorio de estos circuitos neuronales, que se localizan en diferentes estructuras dentro del sistema nervioso central. Los CPGs están compuestos por pequeños grupos de neuronas acopladas sinápticamente con actividad autónoma.

La mayoría de CPGs tienen una arquitectura de red no abierta, es decir, mantienen una topología de conexión en la que cada neurona recibe por lo menos una sinapsis de otra neurona o de otros CPGs o músculos que los CPGs controlan (Huerta *et al.*, 2001; Stiesberg *et al.*, 2007). La arquitectura del CPG más simple es un circuito oscilador de neuronas inhibidoras recíprocas (Miller and Selverston, 1982; Selverston, 2010). Este tipo de conexiones entre neuronas conducen a la regularización del comportamiento colectivo de las mismas. Estas neuronas de forma aislada se comportan de manera individual cuando interactúan entre sí.

Los CPGs son responsables del control rítmico de actividades motoras como caminar, respirar y masticar entre otros (Selverston, 1999; Weimann *et. al.*, 1991; Katz, 2016). Su funcionamiento rítmico se debe a propiedades intrínsecas de las neuronas que lo constituyen y/o a la configuración del circuito. Las neuronas de los CPGs habitualmente muestran un

comportamiento spiking-bursting, con una dinámica muy rica que les permite generar bursts con diferentes períodos de duración, fase y estructura temporal de spikes (Abarbanel *et al.*, 1996; Elson *et al.*, 1998), para estimular la función motora (Grillner, 2003; Marder and Bucher, 2001; Selverston, 2010). Esta rica dinámica proporciona al CPG flexibilidad y robustez para negociar ritmos en función de las entradas externas.

Muchos de los CPGs son redes multifuncionales, capaces de cambiar de un comportamiento a otro dependiendo de las circunstancias particulares, bajo las cuales el circuito está funcionando (Berkowitz *et al.*, 2010; Flamm and Harris-Warrick, 1986; Jing and Weiss, 2001; Latorre *et al.*, 2013; Norekian and Satterlie, 1996; Stein, 2005). Los CPGs son modelos biológicos valiosos para investigar y comprender la dinámica neuronal (Katz *et al.*, 2013; Marder and Bucher, 2001).

Los descubrimientos realizados en estas simples redes neuronales han demostrado ser generalizables a redes más complejas, sea en invertebrados y/o en vertebrados. Debido a las muchas similitudes entre dichos sistemas, especialmente con respecto a los principios básicos de la función neuronal (Marder and Bucher, 2007). Esto proporciona una visión esencial de cómo operan los circuitos neuronales en el sistema nervioso central (SNC) de los vertebrados, que son más grandes y menos accesibles y permite explicar las propiedades computacionales del sistema nervioso (Marder and Bucher, 2007; Selverston, 1999; Selverston, 2010). Los CPGs son capaces de producir patrones estables para generar movimientos coordinados y ritmos estereotipados (Dickinson, 2006; Kiehn and Kjaerulff, 1998; Lafreniere-Roula and McCrea, 2005; Marder and Bucher, 2001; Martínez-Silva *et al.*, 2014; Niu *et al.*, 2014; von Euler, 1983; Weaver *et al.*, 2010; Zhong *et al.*, 2012) que contribuyen significativamente a la comprensión actual de cómo operan los circuitos motores rítmicos a nivel celular.

Dos de los CPGs más conocidos y detallados se localizan en el ganglio estomatogástrico del sistema nervioso estomatogástrico de los crustáceos, utilizados para estudios neuronales. Estos circuitos son el CPG gástrico y el CPG pilórico (Harris-Warrick *et al.*, 1992; Hartline, 1979; Hartline and Maynard, 1975). Estos CPGs exhiben una amplia gama de ritmos y son los responsables de las acciones motoras del estómago (Selverston and Ayers, 2006).

El CPG gástrico es un sistema neuronal muy estudiado, su estructura y funcionalidad son conocidas detalladamente (Mulloney and Selverston, 1974; Selverston and Mulloney, 1974; Hartline and Maynard, 1975; Hartline and Gassier, 1979; Selverston and Moulins, 1987; Harris-Warrick et al., 1992). La función del ritmo gástrico es coordinar el movimiento de los dientes gástricos, para masticar los alimentos en la muela gástrica (Selverston, 2008). En cambio, el ritmo pilórico es el responsable de la contracción de los músculos que filtran y bombean los alimentos del estómago al intestino (Selverston, 1988), por medio de la relajación y la contracción de forma periódica, ajustando su velocidad (Selverston and Ayers, 2006).

De acuerdo al comportamiento observado, los patrones de actividad generados en los músculos estomacales consisten de estímulos bursting. La actividad bursting en las motoneuronas del CPG pilórico están claramente asociadas con la contracción del músculo, que es insensible a pequeños cambios en el intraburst (Morris and Hooper, 1997). Estudios realizados en diferentes sistemas estomatogástricos, como el de la langosta californiana (*Panulirus interruptus*) y el cangrejo de mar (*Cancer borealis*), han revelado la presencia de mecanismos neuronales que permiten generar patrones motores rítmicos, debido a que son relativamente sencillos de aislar y alterar, tanto *in vivo* como *in vitro* (Bidaut, 1980; Marder and Eisen, 1984; Mulloney and Selverston, 1974), ya sea, por el número reducido de neuronas que conforman el sistema y/o por el tamaño (son comparativamente grandes), respecto a otros

animales, lo que facilita su manipulación e identificación. La importancia del estudio del ganglio estomatogástrico radica en el conocimiento de sus propiedades celulares y sinápticas, mismas que se encuentran en todos los sistemas nerviosos, incluyendo el cerebro de los mamíferos (Selverston, 2008).

Estudios recientes en preparaciones *in vitro* (Szucs *et al.*, 2003; Szücs *et al.*, 2005) han demostrado que la distribución temporal de los potenciales de acción intraburst (IBSPs) son específicos para cada tipo de célula del CPG estomatogástrico de los crustáceos, que coexiste en su ritmo lento y son capaces de reflejar cambios de acuerdo a los patrones de conectividad de la red. Esto implica un posible papel funcional en la codificación de la información.

Firmas Neuronales

La actividad spiking-bursting ha sido objeto de múltiples estudios en sistemas biológicos, siendo su tipología muy variable. Dependiendo del sistema estudiado o del instante en que se registre la actividad de la célula, pueden observarse patrones spiking-bursting repetitivos muy robustos, o ráfagas con un comportamiento incluso caótico (Aihara and Matsumoto, 1986; Hayashi and Ishizuka; 1992, Elson *et al.*, 1998; Varona *et al.*, 2001b). En algunos sistemas neuronales, las ráfagas de potenciales de acción generadas por cada una de las neuronas que los componen son muy precisas y a la vez tan diferentes entre sí, por lo que, el patrón temporal de sus spikes ha recibido el nombre de firma neuronal, ya que es tan particular y discriminatorio que permite identificar unívocamente a la neurona que emitió la ráfaga, es decir, la fuente de la señal. Estas estructuras temporales tan precisas originalmente se describieron por primera vez en las neuronas del CPG pilórico del sistema nervioso estomatogástrico de la langosta (Szucs *et al.*, 2003; Szücs *et al.*, 2005), aunque posteriormente también se han descubierto en neuronas subtalámicas (Garcia *et al.*, 2005), en células ganglionares de la retina de los mamíferos (Zeck and Masland, 2007) o en las motoneuronas del CPG que controla los latidos del corazón de la sanguijuela (Campos *et al.*, 2007). Además, se han descubierto otros patrones de disparo estereotipados característicos en otros circuitos neuronales que pueden exhibir firmas neuronales funcionales o conductuales, que representan diferentes estados asociados a la tarea realizada en un momento dado (Klausberger et al., 2003; Somogyi and Klausberger, 2005; Kaping et al., 2011). La observación de distintas firmas en diferentes sistemas neuronales de vertebrados e invertebrados parece ser relevanté para los circuitos en los que aparecen y pueden tener un significado funcional.

Experimentos recientes han revelado que la distribución temporal de potenciales de acción dentro de las ráfagas (IBSP del inglés *Intra-burst Spike Patterns*) generados por una misma neurona del CPG pilórico de la langosta (Szucs *et al.*, 2003; Szücs *et al.*, 2005) son siempre muy similares y reproducibles en diferentes preparaciones. Por ejemplo, la Figura 4 presenta la actividad de dos neuronas: la neurona PD (panel A) y la neurona LP (panel B) del CPG pilórico de la langosta, registradas en preparaciones in vitro (Szucs et al., 2003). Aquí se muestra la superposición de multitud de ráfagas que, mediante el alineamiento de ráfagas haciendo coincidir al primer spike de cada una de ellas, podemos observar dos cosas. La primera que tan similares son las ráfagas generadas por la misma neurona, observe LD con LD y LP con LP con una pequeña variación al final de la ráfaga. Y que tan diferentes son las ráfagas generadas por las dos neuronas LD y LP.

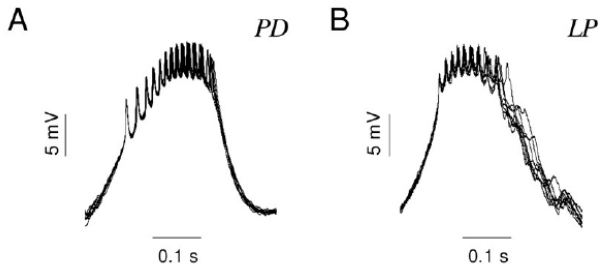

Figura 4. Mediante el alineamiento de ráfagas generadas por una misma neurona del CPG pilórico de la langosta, haciendo coincidir al primer spike de cada una de ellas, se observa que la distribución temporal de potenciales de acción es muy similar, y a la vez muy diferente entre las generadas por diferentes neuronas. La figura ilustra este hecho mostrando la superposición de múltiples ráfagas de las neuronas PD (panel A) y LP (panel B) registradas en preparaciones *in vitro* (Szucs *et al.*, 2003).

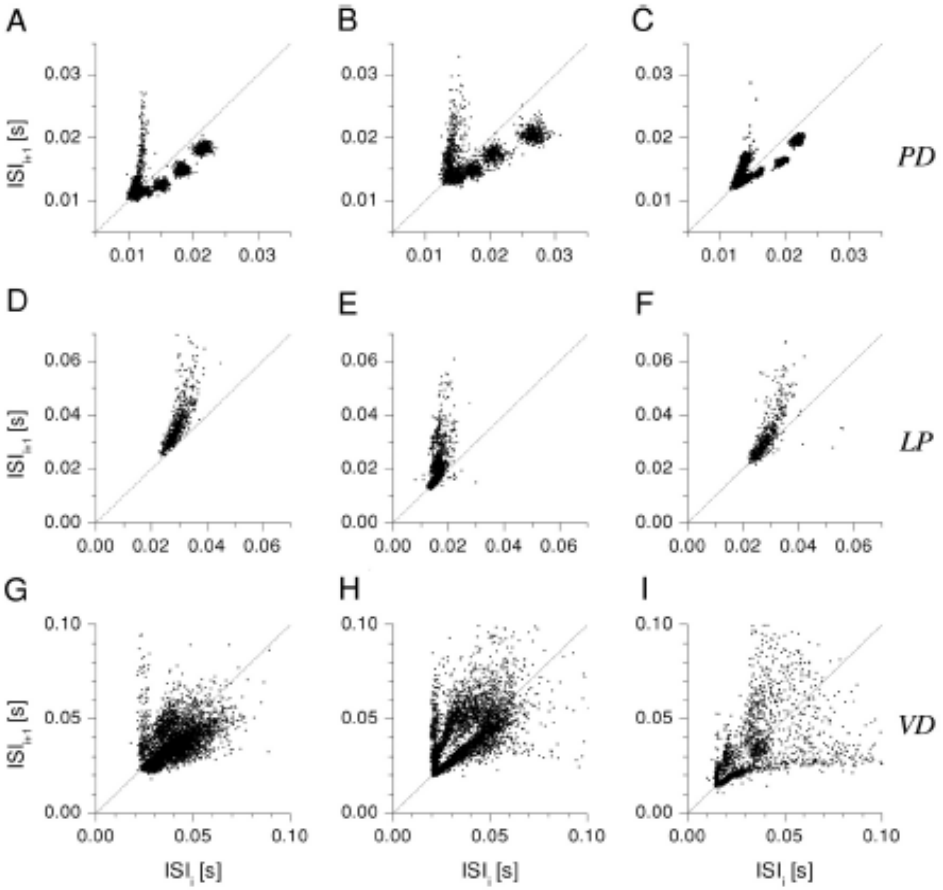

Figura 5: Mapas de retorno de ISIs de las neuronas PD, LP y VD en distintas preparaciones in vitro del CPG pilórico de la langosta (Szucs *et al.*, 2003). En cada una de las filas se corresponde con la medición de tres neuronas diferentes. Visualmente se puede distinguir las similitudes de las firmas de una misma neurona y las diferencias en neuronas distintas.

Visualmente las firmas neuronales pueden caracterizarse a través de mapas de retorno ISIs (del inglés *InterSpike Interval*) que representa el intervalo de tiempo que ocurre desde que una neurona genera un potencial de acción hasta que produce el siguiente, ISIn frente al ISIn+1 (Dekhuijzen and Bagust, 1996; Segundo *et al.*, 1998; Kepecs and Lisman, 2003; Izhikevich *et al.*, 2003). En la figura 5 se representan los mapas de retorno ISIs de tres neuronas

diferentes del CPG pilórico de la langosta. Las neuronas PD (panel superior), LP (panel central) y VD (panel inferior) medidas en distintas preparaciones *in vitro*, del CPG. Estos mapas registran las diferencias en la firma de cada una de estas tres neuronas, así como, la similitud de la firma de una misma neurona en diferentes experimentos. En el caso concreto del CPG pilórico de los crustáceos, los ISIs son reproducibles y permiten identificar de manera única a la neurona emisora de la señal. Esta representación permite caracterizar la forma en que se generan los potenciales de acción dentro de las ráfagas, facilita la clasificación de las neuronas con comportamiento bursting.

Las firmas neuronales coexisten dentro de la información codificada, en otros aspectos de la señal spiking-bursting. Por ejemplo, en el CPG pilórico de los crustáceos las firmas neuronales coexisten en el ritmo lento de la señal generada (Szucs *et al.*, 2003; Szücs *et al.*, 2005). Desde el punto de vista biológico, todavía no está claro si las firmas neuronales tienen algún significado funcional. Esto hace que nos preguntemos si el sistema nervioso podría utilizar esta información como mecanismo de procesamiento y codificación de información neuronal.

Estudios teóricos (Latorre, 2008) muestran que las firmas neuronales pueden participar en una estrategia de codificación multicódigo, en la que, en una misma señal se multiplexen distintos tipos de información. Este tipo de estrategias permitiría al receptor de la señal neuronal determinar el "quién" y el "qué" de la información (Latorre, 2013; Latorre *et al.*, 2006; Latorre *et al.*, 2007), lo que le proporcionaría la capacidad de discriminación y/o contextualización de la información recibida dentro de un burst (Latorre *et al.*, 2004; Latorre *et al.*, 2006). La discriminación permitiría procesar o no los mensajes recibidos, dependiendo del emisor de los mismos. En cambio, la contextualización permitiría procesar la información de distinta forma en base al origen del mensaje, realizando una tarea diferente en función de su contexto (Baroni *et al.*, 2010; Latorre *et. al.*, 2006; Latorre, 2008).

El estudio del procesamiento de información basado en la emisión y reconocimiento de firmas neuronales no ha sido investigado en profundidad. Únicamente existen algunos estudios teóricos preliminares utilizando estos mecanismos, los cuales han proporcionado resultados interesantes (Latorre *et al.*, 2007; Tristán *et al.*, 2004). En el trabajo realizado por Tristán *et al.*, (2004) se propone un modelo simple de red de neuronas para estudiar la capacidad de esta red para procesar la información basada en la emisión y el reconocimiento de firmas neuronales específicas. Los resultados obtenidos muestran propiedades complejas de auto-organización y una amplia capacidad de procesamiento. En el trabajo realizado por Latorre *et al.* (2007), se estudia la capacidad de un modelo de CPG para reaccionar a firmas neuronales a través de sinapsis excitatorias. Los resultados sugieren que las firmas neuronales pueden ser parte de un mecanismo para inducir cambios rápidos en el ritmo generado por un CPG.

Las firmas neuronales que permiten identificar la fuente de la señal pueden ser un mecanismo utilizado por el sistema nervioso para contextualizar o discriminar la información neuronal. El procesamiento de información basado en este reconocimiento puede utilizarse para decidir o ponderar la decisión sobre la salida de una neurona. De confirmarse la existencia de mecanismos de procesamiento de información basados en firmas en el sistema nervioso su potencia computacional se vería incrementada muy significativamente. En este escenario, cobra especial interés el desarrollo y análisis de modelos teóricos de redes neuronales basadas en firmas. Estos modelos ayudarían, en gran medida, a validar la viabilidad teórica de posibles estrategias de codificación y procesamiento de información neuronal. Y así comprender y

analizar la capacidad de las redes basadas en la generación y reconocimiento de firmas. El conocimiento adquirido con dichos modelos podría emplearse para ampliar el paradigma de las redes neuronales artificiales conocido como Signature Neural Networks (Latorre *et al.*, 2011), por lo que es necesario el estudio exhaustivo de posibles mecanismos de procesamiento de información.

Justificación

Uno de los principales objetivos de la neurociencia es la comprensión de los mecanismos que subyacen en la codificación y procesamiento de información basados en la actividad neuronal. Los avances producidos en el estudio del sistema nervioso, en los últimos años, han proporcionado una ingente cantidad de nuevos datos relativos a los mecanismos de codificación, transformación, coordinación, creación, ejecución y aprendizaje de información en distintos tipos de redes neuronales biológicas (Rabinovich *et al.*, 2006). Se piensa que la codificación y procesamiento de información ocurre de diferentes maneras y en diferentes niveles de complejidad y abstracción (Fletcher *et al.*, 2008). En base al modelado de redes neuronales y de neuronas se puede integrar el análisis matemático y las simulaciones por computador con la neurociencia experimental, lo que contribuye significativamente a la comprensión de mecanismos de codificación y procesamiento de información.

Los estudios en este campo no se limitan únicamente al ámbito teórico, sino que permiten su proyección en aplicaciones biomédicas y tecnológicas. Un ejemplo son las redes neuronales artificiales que están inspiradas en sus equivalentes biológicos. Sin embargo, esta bio-inspiración, en la mayoría de los casos, se limita a los conocimientos sobre el procesamiento de la información neuronal disponible desde hace más de 60 años. Los paradigmas de redes neuronales artificiales más tradicionales no hacen uso de los descubrimientos recientes de la neurociencia, los cuales ofrecen nuevos elementos de inspiración. Sólo en los últimos años las nuevas estrategias de procesamiento de información bio-inspiradas han sido tomadas en cuenta para la definición de nuevos paradigmas de redes neuronales artificiales, dando lugar a una nueva generación de estos. Se ha demostrado que algunos de estos paradigmas pueden ser aplicados de forma exitosa y eficiente en la solución de problemas de disciplinas muy diversas (Maas, 1997a; Maas, 1997b; Ruf and Schmitt, 1998; Michie *et al.*, 1994; Bishop, 1995). Uno de estos paradigmas son las redes neuronales basadas en firmas neuronales, que hacen uso de firmas neuronales para identificar de forma inequívoca cada neurona de la red (Latorre *et al.*, 2011). Hasta la fecha se han realizado muy pocos estudios sobre mecanismos celulares que permiten identificar el origen de una señal neuronal, y/o estudios sobre el procesamiento de información basado en el reconocimiento y emisión de firmas neuronales. Sin embargo, los pocos trabajos realizados han proporcionado buenos e interesantes resultados (Latorre 2008; Latorre *et al.*, 2011; Tristán *et al.*, 2004). A pesar de ello, no se ha profundizado en el estudio de las propiedades computacionales de las redes basadas en firmas neuronales. Esto requiere de estudios teóricos y computacionales más detallados.

Objetivos y Procedimientos

El objetivo principal de este trabajo de investigación es el estudio de posibles mecanismos de codificación y procesamiento de información basados en la existencia de firmas neuronales

individuales, así como posibles implicaciones y aplicaciones de este tipo de procesamiento, tanto para los sistemas biológicos en los que se han identificado las firmas neuronales, como en el contexto de las redes artificiales. Para ello, hemos definido modelos con distinto grado de realismo, en los que las neuronas tienen la capacidad de firmar sus señales de salida. Con estos modelos, tratamos de dar respuesta a una serie de preguntas de investigación como:

i) Si un sistema neuronal tiene la capacidad de identificar el origen de sus mensajes de entrada en función de estas firmas, podría realizar un procesamiento de la información más complejo y selectivo.

ii) Si la existencia de firmas neuronales específicas puede no solo permitir a una neurona postsináptica contextualizar sus mensajes de entrada y reaccionar de forma específica a entradas procedentes de determinados emisores, sino también detectar y reaccionar de forma altamente selectiva a secuencias de activación específicas.

Los experimentos y resultados propuestos en esta memoria de tesis doctoral se basan en el diseño e implementación de distintos modelos de neurona, sinapsis y/o red. En todos los casos, se ha realizado una implementación ad-hoc de los modelos en lenguaje C y/o C++. En el caso de aquellos modelos en el que se usan sistemas de ecuaciones lineales, todas se resolvieron numéricamente con el método Runge-Kutta6(5) de paso variable con una tolerancia máxima de 10–15.

A continuación, se presentan los objetivos específicos y los procedimientos a implementar para alcanzarlos, a través del desarrollo de los capítulos de esta tesis.

- **Capítulo 1:** Este primer trabajo de investigación se basa en el modelo simple de red de neuronas que son capaces de reconocer y emitir firmas, con una topología regular, propuesto por Tristán *et. al.* (2004), con la finalidad de ampliarlo y estudiarlo, desde distintas perspectivas, se adicionan distintas topologías de red así como se hace un estudio detallado de las dinámicas colectivas de red.
  El objetivo es analizar la dinámica emergente y las propiedades autoorganizativas con distintas topologías de red, para determinar si el tratamiento de información basado en esta identificación podría ser una potencial estrategia de procesamiento y codificación de información para sistemas neuronales.
  Para ello, se reproduce el modelo simple de red de neuronas (50x50) (Tristan *et al.*, 2004). Cada neurona de la red es capaz de reconocer y emitir firmas. Una firma se define mediante una secuencia de unos y ceros (5 bits). La información se codifica mediante unos y ceros. El comportamiento individual de una neurona está dado por simples reglas de procesamiento y la forma en la cual cada neurona se conecta con otras. Las reglas permiten una discriminación local de información basada en el reconocimiento de las firmas que se reciben por sus canales de entrada (ocho) que están orientadas a determinar la secuencia de bits que se emitirá en los siguientes pasos de tiempo por sus canales sinápticos. Cada neurona reconoce una firma a través de una memoria transitoria (llamada contexto de información local), que permite realizar un seguimiento, en cada paso de tiempo, de las entradas anteriores. Si la neurona reconoce la firma, esta se emite con una cierta probabilidad de reconocimiento (p_r). Caso contrario, se emite una firma espontánea con

una cierta probabilidad (p_e). Después de la emisión, las neuronas tienen un período de refracción (figura 1.1), durante el cual no emite ni reconoce ninguna firma. La conexión entre neuronas se basa en las topologías regulares, aleatorias y small world. Las redes con topología regular se construyen a partir de la conexión de una neurona con sus vecinas más cercanas. En el extremo contrario, las topologías aleatorias se construyen mediante la conexión de una neurona con cualquier otra de la red. En el caso de las topologías small world se encuentran entre lo regular y lo aleatorio.

En este modelo, en primer lugar, se realizan simulaciones con redes autónomas para estudiar su actividad intrínseca cuando no se inyectan estímulos. Posteriormente se estudian redes con diferentes topologías donde se introduce un único estímulo externo a la red. Para caracterizar la dinámica colectiva de la red nos basamos en la evolución del número de neuronas que emiten una firma en un instante de tiempo, sea esta espontánea o introducida. Esto permite estimar propiedades de la red, tales como: su capacidad de procesamiento (número promedio de neuronas que emiten cada firma por unidad de tiempo), la velocidad de propagación de la información (número promedio de neuronas que emiten una firma externa por unidad de tiempo, desde el momento en el que se estimula la red hasta que se alcanza el nivel máximo de procesamiento de esa firma), la capacidad de memoria de la red (capacidad de la red para almacenar una firma externa), y la forma en que la información se propaga por la red (local o globalmente). Un punto de mayor interés en nuestras simulaciones son las respuestas de la red a múltiples estímulos. Para ello, se compara la dinámica colectiva de redes en las que se introduce diferentes estímulos tanto en serie como en paralelo. Las simulaciones con estimulaciones en serie permiten estudiar la competencia entre estímulos que se reciben próximos en el tiempo. Las estimulaciones en paralelo permiten estudiar la capacidad que tiene la red para procesar y almacenar varios estímulos simultáneamente.

- **Capítulo 2:** En este trabajo, siguiendo la lógica de la investigación, se verificará si los resultados obtenidos en el anterior modelo se pueden replicar, en un modelo más aproximado a un modelo realista. Cada neurona tiene una firma y diferentes modalidades de codificación de información. Las neuronas de los CPGs muestran un comportamiento spiking-bursting en el que tradicionalmente se pensaba que se codificaba la información en la frecuencia de las ráfagas. Por lo tanto, se plantea la hipótesis que se puede codificar información adicional en las firmas.

  El objetivo de este capítulo es estudiar la aplicabilidad del paradigma de redes neuronales basadas en firmas y los posibles mecanismos de codificación y procesamiento de información, en un modelo de red con neuronas tipo spiking. Las redes de neuronas basadas en firmas neuronales, a pesar de estar inspiradas en estructuras temporales precisas, no son redes neuronales artificiales tipo spiking. Esto permitiría determinar si es posible proporcionar propiedades computacionales adicionales a las redes neuronales tipo spiking.

  Se adaptan las características del paradigma de redes neuronales basadas en firmas en un modelo simple de red de neuronas tipo spiking (50x50), con topología regular. Para describir el comportamiento individual de cada unidad hemos definido un modelo estocástico en el que la actividad neuronal se considera como una actividad discreta y está caracterizada en el tiempo por su potencial de membrana, determinada por la probabilidad p. Cada neurona tiene asociada una firma neuronal intraburst que permite su

identificación inequívoca para el resto de las células. Las neuronas son capaces de codificar información de las señales que se emiten en su dinámica lenta (modalidad de codificación de frecuencias) y en su dinámica rápida (modalidad de codificación de firmas), y se usa la plasticidad subcelular para contextualizar o discriminar de forma local los datos recibidos por una unidad. Por tanto, se analizan las dinámicas colectivas emergentes en dos dimensiones de información. Cada neurona reconoce una firma a través de una memoria transitoria (contexto de información local) que permite realizar un seguimiento de la información recibida durante una determinada ventana de tiempo. Por cada spike de entrada, la neurona almacena en su contexto de información local el tiempo en el que se generó el spike y el canal de entrada, para posteriormente comprobar si el patrón de spikes recibido a través del canal de entrada correspondiente aparece en su contexto de información local tantas veces como un umbral de aprendizaje dado. Si esto sucede, el receptor reconoce esta firma, haciéndose parte del patrón de salida de la neurona. Utilizamos la plasticidad subcelular como medio para sincronizar la dinámica intrínseca de la red y dar forma al cálculo de la respuesta de salida en función de la información recibida. Para caracterizar la dinámica colectiva de red en la modalidad de codificación de frecuencias utilizamos la Transformada Wavelet Discreta DWT. En cambio, en la modalidad de codificación de firmas, al igual que el modelo anterior, nos basamos en la evolución del número de neuronas que emiten una firma dada en un instante de tiempo.
En este trabajo, se realizan simulaciones con redes autónomas para estudiar su actividad intrínseca en cada dimensión cuando no se inyectan estímulos. Posteriormente se analizan simulaciones en donde se introduce un único estímulo externo a la red. Y, finalmente, se estudian simulaciones cuando múltiples estímulos se introducen a la red.

- **Capítulo 3:** En este trabajo vamos a utilizar un modelo de neurona más realista, un modelo biofísico de tipo Hogdkin Huxley, que permita a la neurona la combinación de firmas en su entrada. Las firmas se identifican en neuronas del CPG, un CPG es un conjunto de neuronas que trabajan de forma rítmica para generar un patrón secuencial coordinado. Se plantea que una neurona lectora puede identificar secuencias de activación.
  El objetivo es estudiar si una neurona lectora sería capaz de detectar secuencias de activación presinápticas específicas, haciendo uso de las firmas neuronales que identifican las señales de entrada del emisor, procesando selectivamente secuencias de actividad específicas en función de las neuronas que participan en la secuencia y en la relación de fase entre sus ráfagas, para determinar si las secuencias de actividad en determinadas condiciones favorecen la aparición de relaciones preferenciales entrada-salida, por medio de firmas neuronales.
  Para estudiar este tipo de respuestas se implementa un modelo de neurona lectora con un comportamiento spiking-bursting. Para ello, modelamos tanto la dinámica de la neurona como la de sinapsis. Para la neurona usamos el formalismo de tipo Hodgkin-Huxley concretamente el modelo de Komendantov-Kononenko, propuesto para modelar el comportamiento de neuronas del CPG del caracol (Komendantov and Kononenko, 1996). Este modelo exhibe una rica dinámica tanto en la onda lenta como en la onda rápida, análoga a la observada en la actividad bursting en diferentes tipos de neuronas vivas (Komarov et al., 2008) para producir ritmos coordinados y cooperativos. Para la sinapsis hemos usado el modelo estático de conductancia de Destexhe, que describe el comportamiento de sinapsis inhibitorias y excitadoras que llegan a una neurona, mediante

un formalismo cinético para modelar la transmisión sináptica por mediación química (Destexhe et al., 1994). Además, este modelo es adecuado para comprobar los efectos de los cambios en los parámetros intra-unidad de la neurona (Blenkinsop, 2013). Con estos modelos de neurona lectora estudiamos su capacidad de procesar diversas firmas recibidas de forma simultánea (o en tiempos cercanos) a través de diferentes canales de entrada y usar la información referente a la relación de fase entre emisores para calcular una respuesta coherente. En este caso, las firmas son impuestas de forma externa. El procesamiento temporal subcelular en la neurona lectora tiene lugar en dos dimensiones simultáneas. Por un lado, surge una contextualización de las señales de entrada, de cada aferente sináptico en la neurona, a través de sus firmas, que permite calcular una respuesta característica en función de la relación de fase entre las diferentes neuronas coordinadas. Y, por otro lado, el procesamiento temporal de los trenes de spikes que llegan a través de diferentes sinapsis. Para caracterizar la actividad de la neurona lectora nos basamos en los rasterplots e histogramas de salida. En este trabajo vamos a analizar la generación de relaciones preferenciales entrada/salida, dependiendo de los tiempos de actividad, en diferentes grupos de células presinápticas.

Estructura de Tesis

Esta tesis se presenta como un compendio de artículos. Consiste de tres artículos publicados en revistas internacionales revisadas por pares (Carrillo-Medina and Latorre, 2015, 2016, 2018). La contribución específica del autor de esta tesis a las publicaciones ha sido: el diseño y discusión de los experimentos y métodos, realizados conjuntamente con el tutor; la implementación de los modelos y simulaciones propuestas; y, la elaboración de los artículos, en conjunto con el tutor de tesis.

La memoria de tesis está organizada de la siguiente manera:

- Introducción: Este capítulo proporciona una visión general de los conceptos biológicos sobre el sistema nervioso que permitan entender las bases de los modelos computacionales desarrollados durante la investigación.

- Capítulo 1: La investigación presentada en este capítulo, se corresponde con la publicación “Neural dynamics based on the recognition of neural fingerprints", José Luis Carrillo Medina y Roberto Latorre. Frontiers in Computational Neuroscience. 2015. DOI: 10.3389/fncom.2015.00033. [JCR 2015: 2.635 Q1, mathematical & computational biology]. En este trabajo se estudian distintas dinámicas colectivas, mediante las simulaciones de un modelo de red de neuronas basadas en la emisión y reconocimiento de firmas neuronales usando diferentes topologías de red, para estudiar posibles mecanismos de codificación y procesamiento de información.

- Capítulo 2: Este capítulo corresponde a la publicación "Implementing Signature Neural Networks with Spiking Neurons", José Luis Carrillo Medina y Roberto Latorre. Frontiers in Computational Neuroscience. 2016. DOI: 10.3389/fncom.2016.00132. [JCR 2016: 1.801 Q2, mathematical & computational biology]. En este capítulo se muestra la aplicabilidad

- del paradigma de redes neuronales basadas en firmas y mecanismos de procesamiento y codificación de información en un modelo de red con neuronas tipo spiking.

- Capítulo 3: Este trabajo ha sido publicado como: "Detection of activation sequences in Spiking-Bursting Neurons by means of the Recognition of Neural Signatures", José Luis Carrillo Medina y Roberto Latorre. Scientific Reports. 2018. DOI: 10.1038/s41598-018-34757-1. [JCR 2018: 4.011 Q1, multidisciplinary sciences]. En este capítulo, proponemos una estrategia de detección de secuencias de activación específicas en un modelo de neurona basada en conductancia mediante el reconocimiento de una combinación de firmas neuronales.

- Síntesis y discusión de resultados, y conclusiones: El último capítulo de esta tesis está dedicado a la síntesis y discusión de resultados, y conclusiones de la investigación realizada.

Capítulos

Capítulo 1

Dinámica neuronal basada en el reconocimiento de firmas neuronales

José Luis Carrillo-Medina y Roberto Latorre

Frontiers Computational Neuroscience 9 (2015):33

RESUMEN

Evidencias experimentales han revelado la existencia de rasgos característicos en los potenciales de acción de diferentes señales neuronales, por ejemplo, se han reportado "firmas" neuronales individuales que identifican al emisor de la señal o "firmas" funcionales que caracterizan tareas específicas. Estas firmas neuronales pueden desempeñar un papel esencial en el procesamiento de la información neuronal, ya que permiten a los receptores discriminar o contextualizar los estímulos entrantes. Este tipo de estrategia de procesamiento podría ser muy poderosa para los sistemas neuronales, ya que incrementaría significativamente su capacidad de codificación y procesamiento. A pesar de ello, no se ha prestado una especial atención al estudio de mecanismos de procesamiento de información basados en la identificación de determinadas firmas neuronales específicas. En este trabajo, estudiamos (i) la dinámica colectiva emergente de una red de neuronas que se comunican entre sí mediante el intercambio de firmas neuronales y (ii) la influencia de la topología de la red en las propiedades autoorganizativas de una red con estas características. En la red surgen dinámicas colectivas complejas en presencia de estímulos. Ciertas entradas predefinidas en forma de una firma neuronal concreta se detectan y codifican como patrones de actividad que coexisten y se propagan a través de la red con diferentes organizaciones espaciales. Los patrones de actividad causados por un estímulo pueden sobrevivir una vez finalizada la estimulación, lo que proporciona mecanismos de memoria a la red. Los resultados presentados en este trabajo sugieren que el procesamiento de información neuronal basado en firmas puede ser una estrategia plausible, flexible y poderosa para el sistema nervioso.

NEURAL DYNAMICS BASED ON THE RECOGNITION OF NEURAL FINGERPRINTS

Abstract: Experimental evidence has revealed the existence of characteristic spiking features in different neural signals, e.g., individual neural signatures identifying the emitter or functional signatures characterizing specific tasks. These neural fingerprints may play a critical role in neural information processing, since they allow receptors to discriminate or contextualize incoming stimuli. This could be a powerful strategy for neural systems that greatly enhances the encoding and processing capacity of these networks. Nevertheless, the study of information processing based on the identification of specific neural fingerprints has attracted little attention. In this work, we study (i) the emerging collective dynamics of a network of neurons that communicate with each other by exchange of neural fingerprints and (ii) the influence of the network topology on the self-organizing properties within the network. Complex collective dynamics emerge in the network in the presence of stimuli. Predefined inputs, i.e., specific neural fingerprints, are detected and encoded into coexisting patterns of activity that propagate throughout the network with different spatial organization. The patterns evoked by a stimulus can survive after the stimulation is over, which provides memory mechanisms to the network. The results presented in this paper suggest that neural information processing based on neural fingerprints can be a plausible, flexible, and powerful strategy.

Keywords Neuron signature · Local contextualization · Local discrimination · Processing based on signal discrimination · Multicoding · Self-organizing neural network

Intraburst neural signatures were first described for the neurons of the pyloric central pattern generator (CPG) of the lobster stomatogastric nervous system (Szücs *et al.*, 2003; Szücs *et al.*, 2005). They consist of very precise spike timings in the bursting activity of some cell-types. Recent experimental findings in this circuit demonstrate that the reproducibility of these neural fingerprints allows us to identify the source of signals with different bursting frequencies and number of spikes per burst, even across different species (Brochini *et al.*, 2011). The existence of intraburst neural signatures has also been reported in other living neurons, such as subthalamic neurons (Garcia *et al.*, 2005), mammalian retinal ganglion cells (Zeck and Masland, 2007) or leech heartbeat CPG motoneurons (Campos *et al.*, 2007). Similarly, other characteristic stereotyped firing patterns have been discovered in other neural circuits. For example, experimental evidence shows that some neural systems can exhibit functional or behavioral neural signatures representing different states or associated to the task performed at a given moment (Klausberger *et al.*, 2003; Somogyi and Klausberger, 2005; Kaping *et al.*, 2011). The observation of different neural fingerprints in widely different vertebrate and invertebrate neural systems suggests that they can have important functional implications for the circuit where they are present. In this vein, model circuits inspired by the pyloric CPG point out that the characteristic collective behavior of this neural circuit can drastically change when the intraburst neural signature of some of its neurons is modified (Latorre *et al.*, 2002; Rodríguez *et al.*, 2002; Latorre *et al.*, 2004).

Neural signatures characterizing specific signals can be a mechanism used by the nervous system to contextualize or discriminate neural information. Information processing based on the recognition of these neural fingerprints can make use of this recognition, for example, to decide or weight the decision about the output of a neuron, or to emit a new neural fingerprint in the output. Theoretical efforts can largely help to address the information processing based on the emission and recognition of neural fingerprints. Beyond the context of CPG circuits, to our knowledge, only a binary model has been proposed with this goal (Tristán *et al.*, 2004).

Additionally, multicoding strategies including intraburst neural signatures have been recently investigated in the context of a spiking neural network (Latorre, in revision). In the present work, we use the same simple approach as Tristán *et al.* (2004) to study how a large-scale network can detect and discriminate specific neural fingerprints (which can be associated to particular spiking features of other neural areas) in its external stimuli and encode this input in its collective dynamics. The goal is to assess the viability of a neural processing strategy using neural fingerprints, as well as to investigate the underlying encoding mechanisms arising in the network. We are particularly interested in the influence of the network topology on the properties of the dynamic organization of the fingerprint-based dynamics. In the existing models (Tristán *et al.*, 2004; Latorre, in revision), only a regular topology has been used as connection pattern in the network. Here, we use a small-world topology, i.e., networks whose units are organized in densely linked groups that are sparsely but reciprocally interconnected. This pattern of connectivity can provide relevant computational properties to the network (Lago-Fernández *et al.*, 2000; Latora and Marchiori, 2001). All the source code used in the simulations reported in this paper can be found in http://www.ii.uam.es/~rlatorre/source_code.tgz.

The ability of the network to encode and process information is related to the detection and propagation of specific stimuli. We first carry out an analysis of autonomous networks and study the self-organizing properties within networks receiving a single external stimulus. Then, we compare the collective dynamics of networks where multiple stimuli are introduced both in series and in parallel. Simulations reveal that the network displays complex self-organizing properties. Fast transitions of the collective activity emerge in response to the arrival of specific neural fingerprints as external input. These responses are organized as localized patterns of activity with different spatial organization that coexist and compete in the network. The parameters that define the subcellular information processing and the specific organization of the connections among neurons tune the self-organizing properties of the network and have a strong influence on its ability to sustain different stimuli. These factors provide short-term and long-term memory mechanisms to store incoming stimuli after the stimulation is over.

METHODS

Single Neuron Model

Using the same approach as Tristán *et al.* (2004), we have built networks of neurons that generate time-discrete binary signals. In these signals, 1 indicates the generation of an action potential in the corresponding time step; while 0 denotes the absence of spikes (Figure 1.1). Each neuron within the network is connected to other neurons according to different network topologies (see Section Network Model). These connections define the input channels of the neuron. Synapses are simple transmission channels that transfer the presynaptic output to the post-synaptic unit without any transducing mechanism. Each unit has an additional channel to introduce external stimuli in the network. This channel behaves like the synaptic channels and, therefore, all the external inputs have the same strength. The external stimulus is repeatedly delivered through the corresponding channel without silent periods between each presentation until the end of the stimulation period.

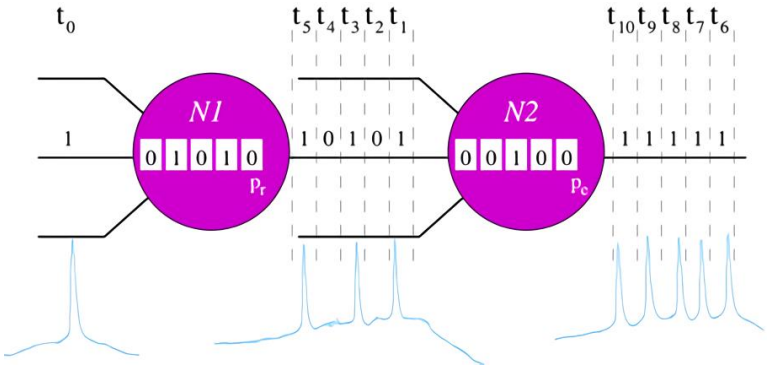

Figure 1.1. Schematic representation of the processing rules in the neuron model. For the sake of simplicity, in this example we only consider an input channel and its corresponding local informational context (sequence of 5 bits represented inside each neuron). In the example, neurons recognize a unique 5-bit neural fingerprint, F = (1, 0, 1, 0, 1), and the spontaneous binary pattern is (1, 1, 1, 1, 1). In time step t_0, the input of the neuron N_1 is 1. The local informational context of this unit indicates that, in the five previous iterations, it has received the sequence (0, 1, 0, 1, 0). Then, when in t_0 the input is processed, N1 recognizes F — i.e., the new local informational context contains the pattern (1, 0, 1, 0, 1). Therefore, in the following five time steps (t_1 – t_5), this neuron emits the serial binary pattern (1, 0, 1, 0, 1) with probability pr. Then, assuming that N_1 emits F, the input of N_2 in time step t_1 is 1. In this case, if we assume that the local informational context of N_2 in this time step is the sequence (0, 0, 1, 0, 0), the neuron does not recognize any fingerprint and emits the spontaneous activity with probability p_e.

Neurons communicate by exchange of serial binary patterns. The information processing in each individual unit is oriented to determine the sequence of bits to be emitted in the following time steps in the output channels. The response pattern is calculated as a function of the detection of specific incoming stimuli. Each individual neuron has the ability to recognize a predefined set of serial binary patterns. These patterns constitute the set of neural fingerprints recognized by the neuron. In response to a recognition, the cell emits a specific output pattern in a probabilistic way. For that, neurons use local informational contexts (Latorre *et al.*, 2001), i.e., local transient memories to keep track of the previous inputs. The size of each local informational context is equal to the length of the neural fingerprints considered in the corresponding simulation. These transient memories allow the implementation of a history-dependent information processing using the following rules (Figure 1.1):

1. Each neuron checks the recognition of a fingerprint using the corresponding local informational context in every time step, i.e., it checks whether the local informational context contains one of its known binary patterns. The external channel is checked first. In this way, the external stimulus has priority over the rest of synaptic inputs. Afterwards, the recurrent connections between neurons are checked randomly.
2. The first recognition of an input fingerprint triggers the emission of this binary pattern with probability p_r (neuron N1 in Figure 1.1). With probability $1 - p_r$, the neuron continues processing as if no recognition happens. The probability p_r varies in the different experiments. Once a neuron starts emitting an output pattern, this cannot be overridden. This implies that if the recognized fingerprint has n bits, no recognition takes place within the following n time steps.
3. If no fingerprint is recognized in a time step, the neuron emits a predefined serial binary pattern with probability p_e (neuron N2 in Figure 1.1), which also varies in the different experiments ($p_e \ll p_r$). This pattern corresponds to the spontaneous activity of the neuron. Note that in this situation, the neuron keeps silent with probability $1 - p_e$.

4. After emission, neurons have a refractory period of 10 time units during which neither emission nor recognition are made.

Probabilities p_r and p_e are subcellular parameters that control, accordingly, the permeability of the neuron to external stimuli and its level of spontaneous activity.

Network Model

Many biological neural networks present structural characteristics that coincide with a small-world topology (White *et al.*, 1986; Scannell *et al.*, 1995; Sporns *et al.*, 2000; Bassett and Bullmore, 2006). These networks fall between regular and random networks. In general, small-world graphs are modeled by two parameters, the connectivity and the randomness of the links (Watts and Strogatz, 1998). The main properties of the small-world networks are that they can be highly clustered like regular networks and, at the same time, have small path lengths like random ones (Watts and Strogatz, 1998; Albert and Barabási, 2002).

In this work, we build small-world networks of 2500 neurons where each unit is connected to eight other neurons. To build these networks, we start with a regular two-dimensional (50×50) grid with periodic boundary conditions where each unit is connected to its eight nearest neighbors. Then, each connection with a neighbor is broken with probability p to connect the neuron with another neuron chosen randomly (Watts and Strogatz, 1998; Lago-Fernández *et al.*, 2000). The value of the rewiring probability p controls the regularity degree in the network, being the limits of regularity and randomness $p = 0$ and $p = 1$, respectively. The small-world topology lies in the intermediate region $0 < p < 1$. As we are interested in the effect of the topological substrate on the self-organizing properties of the network, we simulate networks with different regularity degrees. In particular, networks with $p = 0$ (regular networks), $p = 0.1$, $p = 0.25$, and $p = 1$ (random networks). Hereafter, we accordingly identify these topologies with the labels "Regular," "SW(10)," "SW(25)," and "Random."

RESULTS

Spontaneous Intrinsic Activity

The network displays intrinsic dynamics, i.e., neural dynamics that do not directly correlate to the dynamics of an external stimulus, related to the emission of the spontaneous activity. In the absence of stimuli, the spontaneous intrinsic activity within the network evolves to a stationary state (e.g., see blue traces in the time series plotted in Figure 1.2 before the arrival of the external stimulus at time step 5000). For simplicity, in the simulations presented in the following sections, neurons do not recognize the spontaneous activity as a neural fingerprint. In this situation, the level of spontaneous intrinsic activity in the network only depends on the value of p_e regardless the network topology (Table 1.1). As expected, the larger the emission probability of the spontaneous pattern, the higher the level of spontaneous intrinsic activity in the network. In simulations where the spontaneous pattern is recognized as a neural fingerprint, the network also reaches a mean steady level of spontaneous activity, but this depends on the corresponding value of p_r too.

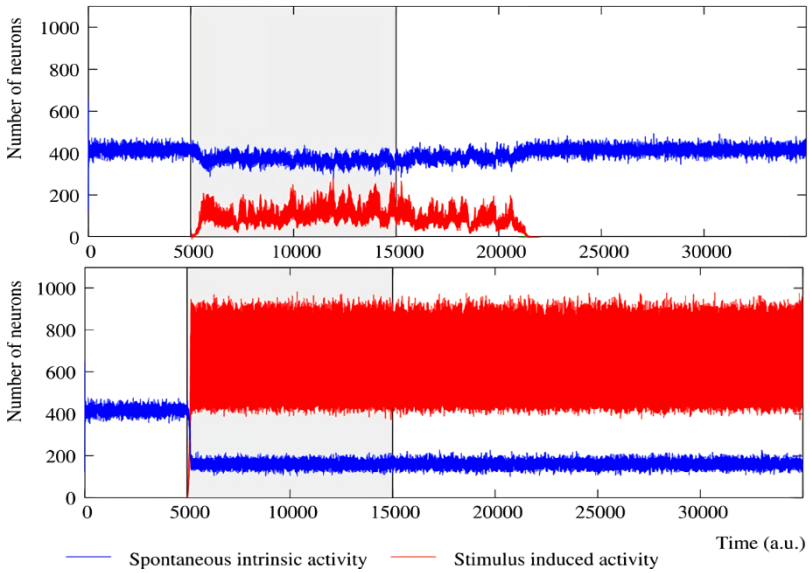

Figure 1.2 Evolution of the collective dynamics of two different networks first without stimuli, then during the stimulation (grayed area) of a randomly chosen neuron with the stimulus (1, 0, 1, 0, 1), and finally without any stimulation again. Results are the same with other 5-bit external stimuli. Blue traces correspond to the spontaneous intrinsic activity. Red traces show the evolution of the number of neurons that follow the external stimulus (i.e., the stimulus induced activity). The figure illustrates some of the different behaviors that the network can exhibit depending on the individual neuron parameters and the network topology (see the text for a detailed description). Top: Example of short-term memory network in which the global activity is nearly constant. This network consists of 2500 units with $p_e = 0.05$ and $p_r = 0.35$ connected with a SW (25) topology. Bottom: Example of long-term memory network in which the external stimulus significantly increases the level of activity in the network. The network consists of 2500 units with $p_e = 0.05$ and $p_r = 0.80$ connected with a SW(25) topology.

p_e	Regular	SW(10)	SW(25)	Random
0.05	416.64 ± 0.15	416.59 ± 0.23	416.52 ± 0.42	416.56 ± 0.24
0.10	576.96 ± 0.17	576.76 ± 0.14	576.95 ± 0.29	577.04 ± 0.38
0.15	661.72 ± 0.21	661.84 ± 0.29	661.68 ± 0.22	661.75 ± 0.22
0.50	833.34 ± 0.03	833.30 ± 0.06	833.33 ± 0.08	833.34 ± 0.06
0.80	869.57 ± 0.01	869.56 ± 0.02	869.55 ± 0.02	869.56 ± 0.03
1.00	882.42 ± 0.00	882.42 ± 0.00	882.42 ± 0.00	882.42 ± 0.00

Mean data are calculated considering 20 simulations with different random seed, spontaneous binary pattern and connectivity. For the same value of P_e, the level of spontaneous intrinsic activity in the network is nearly the same for all the network topologies. Note now precise are there values. If the spontaneous pattern has a different number of bits (from 4 to 11), results are equivalent.

Table 1.1. Mean number of neurons that emit the spontaneous activity (5 bits) per time step in autonomous networks of 2500 units with a given value of p_e as a function of the network topology.

Detection of External Stimuli

Neurons communicate by exchange of serial binary patterns. The ability of the neural network to process information based on the emission and recognition of neural fingerprints is related to the detection and propagation of specific serial patterns received through the input channels. In this section, we study the self-organizing properties of networks that receive a single

stimulus, analyzing how the intraunit parameters and the network topology tune the collective neural dynamics. By default, a neuron emits a predefined spontaneous pattern. This output pattern only changes when the neuron recognizes an incoming fingerprint. In order to analyze the reverberating patterns sustained by the network and characterize the network collective dynamics, we compute during a period of time the overall number of neurons that recognize and emit a given neural fingerprint per time unit. This measure provides an estimation over time of the level of activity in the network related to each neural fingerprint. Results reported here correspond to simulations in which the network initially evolves freely and, then, the pattern (1, 0, 1, 0, 1) is introduced as external input in a randomly chosen neuron. In our first analysis, this neural fingerprint is the only pattern that neurons are able to recognized.

The simulations point out that the ability of the network to sustain the fingerprints detected in the incoming input is related to a competition between the spontaneous intrinsic dynamics and the dynamics evoked by the arrival of the external stimulus. This competition depends on a trade-off between the degree of spontaneous activity in the network and the permeability of each individual neuron to stimuli. These properties are driven, accordingly, by probabilities p_e and p_r. In the case of external stimuli of 5 bits, when p_r is lower than 0.30 or p_e is too high (see Table 1.2), the spontaneous intrinsic dynamics wins the competition and only the nearby neurons to the stimulated unit detect the stimulus. Thus, no significant changes are observed in the network collective activity. Table 1.2 compares the maximum value of p_e that allows networks with different p_r values to process 5-bit stimulus arriving to a single neuron. If the value of p_e is above this threshold, the external stimulus does not spread through the network. The higher the value of p_r, the larger the corresponding threshold of pe. This relation points out that the competition between the spontaneous intrinsic dynamics and the stimulus induced dynamics is the basis of the fingerprint-based encoding. However, the trade-off between probabilities p_r and p_e varies with the network topology. For a given value of p_r, we observe that the corresponding threshold of p_e grows with the network randomness (Table 1.2). This result indicates that random connections facilitate the detection and propagation of stimuli in the sense that their presence increases the "effort" required by the spontaneous intrinsic dynamics to win the competition with the stimulus induced dynamics.

p_r	Regular	SW(10)	SW(25)	Random
0.30	0.01	0.03	0.04	0.04
0.50	0.07	0.09	0.10	0.11
0.80	0.15	0.18	0.20	0.21
1.00	0.20	0.25	0.26	0.28

This value is the same regardless the predefined sequence of 5 bits used as external stimulus. Above this threshold, the network does not detect external stimuli. In the same way, when $p_r < 0.30$, it does not detect the stimulus independently of the p_e value.

Table 1.2 Trade-off between the values of p_e and p_r that allows networks of 2500 units to detect 5-bit stimulus introduced into one neuron.

The most interesting cases from the information processing perspective are those where external stimuli propagate through the network. In these networks, a fast transition of the collective activity occurs when the stimulation begins and new collective dynamics emerges

as a function of the incoming stimulus (Figure 1.2 at time step 5000). If we analyze the global level of activity in the network in these simulations, we observe that the preferred binary pattern reverberating in the network can follow the external stimulus. When the external stimulus arrives, the number of neurons that recognize and emit the corresponding neural fingerprint—i.e., the neurons that follow the stimulus—grows, while the spontaneous intrinsic activity drops. During the stimulation period (grayed area in Figure 1.2), the network evolves to a stationary state in which the stimulus induced activity fluctuates around a steady level. This steady level of activity is characteristic of the network (by network we mean the combination of network topology and intraunit parameters) and does not depend on the duration of the stimulation period. Therefore, it can be used to quantitatively characterize how external stimuli are detected and propagate through the network. As an example, Table 1.3 shows the corresponding characteristic value for different networks of neurons with a fixed value of p_e receiving a single 5-bit stimulus. As expected, the higher the permeability of each individual unit to external stimuli (given by p_r), the greater the number of neurons that follow the incoming stimulus. For the same network topology, the activity evoked by this stimulus can even be increased more than 100% by simply modifying the value of p_r. For instance, in the regular network case, the mean number of neurons following the stimulus in simulations with $p_r = 0.5$ and $p_r = 0.8$ is around 275 (≈ 11% of the neurons in the network) and 532 (≈ 21% of the neurons), respectively. As we have already shown above, unlike the spontaneous intrinsic activity, the activity evoked by stimuli also depends on the network topology. The higher the number of random connections, the larger the detected fingerprint emission level —i.e., network randomness has a similar effect to increasing the permeability of individual neurons to external stimuli (Table 1.3). This results in an enhancement of the ability of the network to sustain incoming stimuli. The increased level of stimulus induced activity with the network topology is more significant for low values of p_r. As probability p_r grows, the level of stimulus induced activity tends to be the same for all the network topologies. For example, the difference between regular and random networks is ≈ 21% with $p_r = 0.5$, ≈ 4% with $p_r = 0.8$ and ≈ 2% with $p_r = 1$.

p_r	Regular	SW(10)	SW(25)	Random
0.50	275.37 ± 1.37	318.54 ± 1.29	334.93 ± 0.96	350.62 ± 0.64
0.80	531.94 ± 0.50	540.17 ± 0.92	545.52 ± 0.57	553.52 ± 0.23
1.00	622.73 ± 0.33	628.85 ± 0.46	634.07 ± 0.56	638.02 ± 0.57

*This value characterizes the level of stimulus induced activity in the network. Fixing p_e at another value, results are equivalent. Keep in mind that in the networks depicted in the table, the minimun value of p_r that allows the network to detect external stimuli is 0.30 (**Table 2.2**). Mean data are calculated using 20 simulations with different random seed, 5-bit stimulus introduced in the network and connectivity.*

Table 1.3 Mean number of neurons that follow the external stimulus per time unit in networks of 2500 units with $p_e = 0.05$ where a single 5-bit stimulus is introduced in a randomly chosen neuron.

In addition to the level of activity induced by the external stimulus, another relevant feature characterizing how information spreads through the network is the stimulus propagation velocity. This can be estimated using the time the network needs to reach its characteristic steady level of stimulus induced activity from the beginning of the stimulation.

Beyond the expected effect of p_r, if we analyze the propagation velocity in networks with an equivalent behavior in terms of level of spontaneous intrinsic activity and stimulus evoked activity (e.g., see Table 1.4), we observe that the higher the network randomness, the faster the stimulus propagation through the network. The difference on the propagation velocity as a function of the network topology can be explained analyzing how stimuli travel through the network. To illustrate the external stimulus propagation, we have generated square-shaped movies representing the evolving network dynamics. In these activity movies, each point in the 50×50 frame represents with a color code the activity of a neuron, i.e., the binary pattern that emits in the corresponding time step. Figure 1.3 shows snapshots of four representative activity movies illustrating how an external stimulus propagates through networks with different topologies. In regular networks (panel A), the stimulus spreads as wave fronts centered in the stimulated unit. Then, to reach the furthest regions, it needs to travel through the whole network. Conversely, in less regular topologies (panels B–D), the stimulus is distributed through the whole network almost from the beginning of the stimulation. This produces several coexisting propagating fronts of information. The presence of a single wave front in regular networks translates into a slower propagation velocity.

Topology	Propagation velocity
Regular	*3.82 ± 0.44*
SW(10)	*13.15 ± 2.11*
SW(25)	*16.88 ± 1.30*
Random	*17.80 ± 1.13*

*Regardless the network topology, these networks achieve nearly the same level of spontaneous intrinsic activity (**Table 1.1**) and stimulus induced activity (**Table 1.3**). With other parameters, results are equivalent but varying the mean propagation velocity. Mean data are calculated considering 100 simulations with different random seed and 5-bit stimulus introduced in the network.*

Table 1.4 Mean external stimulus propagation velocity (neurons/time) as a function of the network topology in networks of 2500 units with $p_e = 0.05$ and $p_r = 0.80$ where a single 5-bit stimulus is introduced in a randomly chosen neuron.

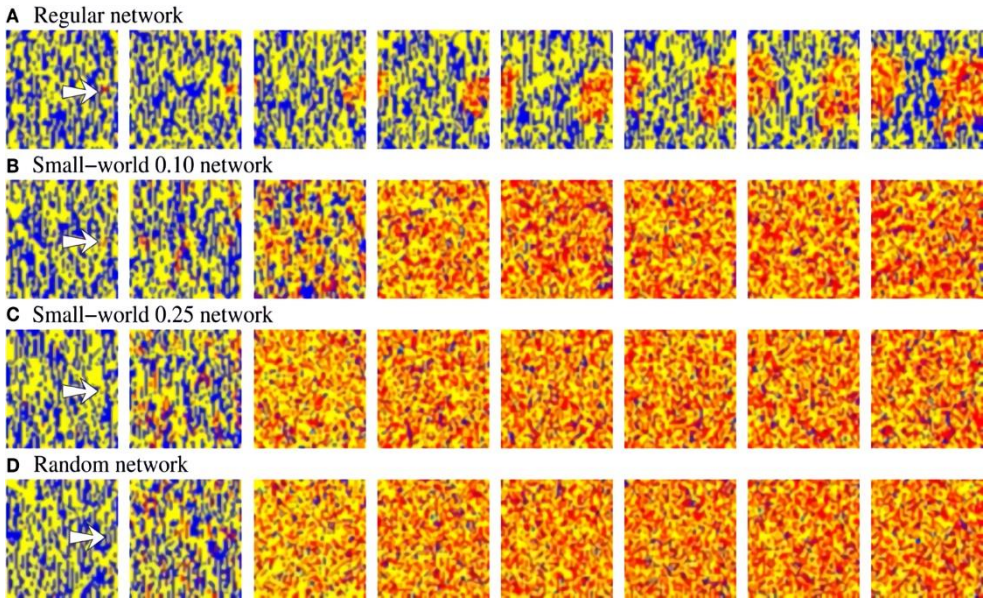

Figure 1.3 Snapshots of four representative activity movies illustrating the external stimulus propagation.

The four networks have an equivalent behavior in terms of level of intrinsic spontaneous activity and level of activity evoked by external stimulus. To better appreciate the difference between the different topologies, we show networks with a high level of stimulus induced activity. Sequences develop in time from left to right with a time interval between frames of 20 a.u. Each point in the 50×50 square represents with a color code the evolution in time of a neuron within the network. Yellow corresponds to silent neurons (i.e., neurons not emitting a specific binary pattern). Blue corresponds to the spontaneous intrinsic activity. Red corresponds to the emission of the pattern associated to the external stimulus. The arrow in the first frames indicates the approximate location of the stimulated neuron. Note that the spontaneous intrinsic activity decreases as a consequence of the propagation of the stimulus until the preferred pattern reverberating in the network follows the external stimulus (in the regular network, this situation is not observed in the snapshots due to the slower propagation velocity).

The activity movies representing the evolving network dynamics point out that not only the level of activity evoked by stimulation characterizes the fingerprint-based encoding. Localized patterns of activity traveling through the network with different spatial organization can be formed due to the external stimulus propagation. These spatio-temporal patterns generated in response to stimuli can remain bounded in a region, can propagate with a fix spatial structure or as transient fronts of information, or can lack a well-defined spatial structure. Figure 1.4 shows a representative example of these spatio-temporal patterns in a network with a lower synchrony degree than in networks depicted in Figure 1.3. The generation of transient patterns of activity is crucial for the detection and encoding of external stimuli because, as we discuss in Section Encoding of Multiple Simultaneous Stimuli, the coexistence of several stimuli within the network is related to the different clusterization and coherence of these stimuli evoked spatio-temporal patterns.

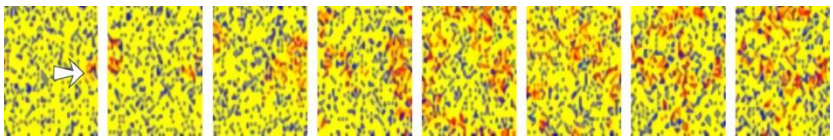

Figure 1.4 Snapshots of an activity movie belonging to the network depicted in top panel of Figure 1.2 The figure illustrates the spatio-temporal patterns generated by the network in response to stimulus. Sequences develop in time from left to right with a time interval between frames of 50 a.u. Color code is the same used in Figure 1.3. The arrow in the first frame indicates the approximate location of the stimulated unit.

Results presented in this section correspond to stimuli of 5 bits introduced in a randomly chosen neuron. In simulations where external stimuli have a different length (from 4 to 11 bits) and/or they are injected in a greater number of neurons (from 2 to 30), results are equivalent to the ones discussed here, but taking into account the following. On one hand, increasing stimulus lengths helps the spontaneous intrinsic activity to win the competition because longer stimuli require more time steps to be detected and, therefore, the probability to emit the spontaneous binary pattern increases. And, on the other hand, a greater amount of stimulated neurons helps the detection process since the level of activity related to the external stimulus grows with the number of stimulation sources.

Network Memory

In the previous section, we have studied the ability of the neural network to sustain external stimuli while they are active. However, an interesting feature of the network is its memory ability, i.e., the ability to sustain a detected pattern in the collective fingerprint-based

dynamics beyond the time period of stimulation. In order to study this property, we have carried out simulations where the external stimulus is introduced in the network just for a while. In these simulations, we study how the stimulus induced activity survives in the network after the end of the stimulation. Taking into account the results described in Section Detection of External Stimuli, we focus on networks able to detect incoming stimuli. Here, we analyze the same simulations as in the previous section, but when at time step 15,000 the stimulation ends—i.e., the network initially evolves freely, then, at time step 5000, the stimulus (1, 0, 1, 0, 1) is introduced into a randomly chosen neuron during 10,000 steps, and, finally, no stimulation is present again (Figure 1.2). Equivalent results to those presented here are obtained in simulations with external stimuli from 4 to 11 bits injected in a greater number of neurons (from 2 to 30).

The level of activity analysis indicates that the network may sustain external stimuli transiently—i.e., the stimulus induced activity reverberates just for a while and then the corresponding binary pattern disappears from the network (short-term memory or working memory)—or persistently—i.e., after the stimulation, the activity evoked by the stimulus coexists with the spontaneous intrinsic activity in a permanent way (long-term memory). Top and bottom panels of Figure 1.2 illustrate, correspondingly, two examples of short-term and long-term memory. In short-term memory networks, the propagation of the external stimulus is a transient effect directly linked to stimulation. Thus, when the stimulation ends and no external input supports the generation of the spatio-temporal patterns encoding the stimulus, the corresponding activity stepwise disappears from the network and the spontaneous intrinsic activity prevails (i.e., the network "forgets" the stimulus). Stimuli usually reverberate in short-term memory networks with a regular topology for longer periods than in random networks, in which stimuli can even disappear almost instantaneously when the stimulation is over. However, no general conclusions can be drawn because the stimulus reverberation period significantly varies even in the same network receiving the same stimulus (cf. transition periods between external stimuli in Figure 1.6). In long-term memory networks, the stimulation produces persistent changes in the network collective dynamics. This leads the network to a new stable state where the reverberation of the patterns associated with the external stimulus is not sustained by stimulation, but it is a network effect. In this way, external stimuli can win the competition and prevail over the spontaneous intrinsic activity (e.g., see final snapshots of Figure 1.3). In these cases, the spontaneous activity does not completely disappear from the network because of the probability of emitting this pattern when no fingerprint is recognized in a time step (p_e).

The factors that determine if the neural network behaves as a short-term or a long-term memory are again related to the competition among the spontaneous intrinsic and the stimulus induced activity. As we have previously discussed in Section Detection of External Stimuli, the mode of competition varies as a function of the relation among the intraunit parameters p_e and p_r and the network topology. To illustrate the relationship between these factors, a phase diagram locating the different behaviors in the space of intraunit parameters for networks with different topologies is shown in Figure 1.5. There is a threshold value of p_r for each value of p_e that determines if the network behaves as a transient (below the threshold) or a persistent memory (above the threshold). Independently of the network topology, as the level of spontaneous intrinsic activity grows, a higher permeability to external stimuli is required to become a long-term memory. Regarding the network topology, random connections contribute to long-term memory mechanisms, unlike regular connections that

help short-term memory mechanisms. In this manner, for example, when $p_e = 0.05$, random enough ($p > 0.80$) small-world networks of 2500 units never behave as a short-term memory.

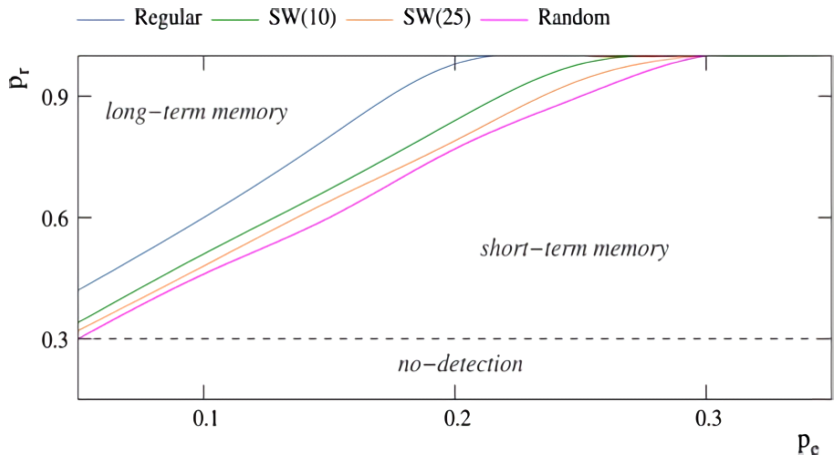

Figure 1.5 Phase diagram showing the regions at which short-term and long-term memory phases appear for networks of 2500 neurons receiving a single 5-bit stimulus. The minimum probability p_r that allows these networks to detect external stimuli is 0.30 (Table 1.2). Each color trace corresponds to networks with a different topology.

Total Activity in the Network

The network can display two different modes of operation according to the evolution of the total level of activity in the network, i.e., the overall number of active neurons whatever the binary pattern they are emitting. In Section Spontaneous Intrinsic Activity, we show that the spontaneous intrinsic activity in autonomous networks reaches a steady level. Similarly, the arrival of a stimulus makes the level of activity related to this external input also reaches a steady level. In these cases, a transition to a lower level of spontaneous activity is produced due to the spreading of the stimulus (see Section Detection of External Stimuli for details). This lower level is also kept constant during the stimulation period. Nevertheless, the total level of activity in the network can be kept nearly constant over time, but also it can be increased due to stimulation (cf. Figure 1.2, top and bottom panel). Networks with a constant level of total activity seem to have a maximum processing capacity in terms of the maximum number of neurons that can be simultaneously active. In the presence of stimuli, active neurons are distributed between the different binary patterns present in the network. The arrival of a stimulus produces a proportional decrease in the spontaneous intrinsic activity as the increase in the stimulus induced activity, and vice versa when the stimulation ends. Only short-term memory networks display this mode of operation. In contrast, when the stimulus increases the level of activity in the network, the number of neurons that follow the stimulus grows faster than the decreasing spontaneous activity. In these cases, the network can sustain the stimulus permanently (as in the example of Figure 1.2) or transiently. In this last situation, once the external stimulus disappears from the network, this recovers the steady level of spontaneous intrinsic activity.

Encoding of Multiple Simultaneous Stimuli

A major point of interest in this study is the network response to multiple stimuli, i.e., the

encoding and coexistence of several neural fingerprints in the network. In this section, we discuss the emerging collective dynamics of networks receiving external stimuli in series (Section Encoding of Multiple Simultaneous Stimuli: In-Series Stimulation) and in parallel (Section Encoding of Multiple Simultaneous Stimuli: In-parallel stimulation). The arrival of multiple stimuli simultaneously or close in time induces the generation of different coexisting patterns of activity within the network. In this situation, a competition between the spatio-temporal patterns encoding the different stimuli arises. In simulations with in-series stimulation, we study the competition between reverberating patterns encoding a previously received stimulus and patterns supported by an active stimulus. This allows us to assess the ability of the network to retain information regarding recent past stimuli (i.e., its transient memory capability) when a new stimulus arrives. Meanwhile, in-parallel stimulation allows studying the ability of the network to sustain several simultaneous stimuli.

To address the effect of network topology on the spatio-temporal activity of the network, we compare the self-organizing properties of "equivalent networks" in terms of spontaneous intrinsic activity (Section Spontaneous Intrinsic Activity), stimuli induced activity (Section Detection of External Stimuli), type of memory (Section Network Memory), and total activity in the network (Section Total Activity in the Network). This allows us to compare networks with different topologies under the same conditions. We discuss here two particular cases of equivalent networks:

- Short-term memory networks with a low level of activity. These networks generate propagating well-defined spatio-temporal patterns to encode incoming stimuli (e.g., see Figure 1.4). Then, one could intuitively expect a slight competition between coexisting spatio-temporal patterns, which a priori must contribute to a better encoding of multiple simultaneous stimuli.
- Long-term memory networks with a high level of activity. When a long-term memory network detects an external stimulus, the corresponding spatio-temporal activity is sustained by the network intrinsic dynamics. Furthermore, a high level of activity induces almost total synchronization over the whole network (e.g., see Figure 1.3). Therefore, under these conditions, a strong competition among coexisting patterns of activity must a priori arise in the network.

In the following sections, we discuss equivalent networks of 2500 neurons with the intraunit parameters shown in Table 1.5 and receiving 5-bit stimuli. For other equivalent networks receiving stimuli of a different length (from 4 to 11 bits), results are equivalent.

Topology	Short-term memory	Long-term memory
Regular	*0.05 – 0.42*	*0,05 - 0.80*
SW(10)	*0.05 – 0.34*	*0,05 - 0.80*
SW(25)	*0.05 – 0.32*	*0,05 - 0.80*
Random	*0.05 - 0.31*	*0,05 - 0.80*

When a network of 2500 units with the parameters of the first column receives a stimulus of 5 bits in a single neuron, its mean level of spontaneous intrinsic activity and level of stimulus induced activity are ≈ 410 and ≈ 120 neurons per time unit, respectively, Therefore, they are equivalent short-term memory networks with a low level of activity. Similarly, networks of 2500 units with the parameters of the second column where stimuli are injected in clusters of 2 x 5 neurons are equivalent long-term memory networks with a high level of activity (their level intrinsic spontaneous activity and their level of stimulus induced activity are ≈ 410 and ≈ 690 neurons per time unit).

Table 1.5 Values of p_e and p_r (respectively, first and second value of each pair) used in the simulations presented

in Sections Encoding of Multiple Simultaneous Stimuli: In-Series Stimulation, In-parallel Stimulation.

In-Series Stimulation

In simulations where the stimuli are in series introduced in the network, we alternate stimulation episodes in which two different external stimuli are injected in the same group of neurons. In the simulations presented here, initially, the network evolves freely. At time step 5000, the stimulation begins. In each stimulation episode, a single stimulus arrives to the network during 10,000 time units. Then, there is an inter-stimulation interval of 5000 time steps where no stimulus is introduced. This sequence is repeated eight times alternating two different stimuli (A and B), which are the two binary patterns recognize by the neurons in the network. Finally, at time step 120,000 no stimulus is introduced any longer. Results are independent of the stimulation patterns and of the location of the neurons that receive the external stimuli.

Equivalent results to the ones described in the previous sections are also produced when the network receives two stimuli in series (see Figures 1.6, 1.7). These results can be summarized in the following points:

- Initially, without any stimulus, the activity of the network evolves to a stationary state where only spontaneous intrinsic activity is present in the network regardless its topology.
- The total activity in the network can be kept constant or be increased due to stimulation depending on the intraunit parameters and the network topology.
- Stimulation evokes collective dynamics in which the spontaneous intrinsic activity competes with the activity induced by external stimuli. Due to this competition, the level of spontaneous intrinsic activity drops.
- When the stimulation is over, reverberating patterns encoding external stimuli can survive within the network transiently or persistently.

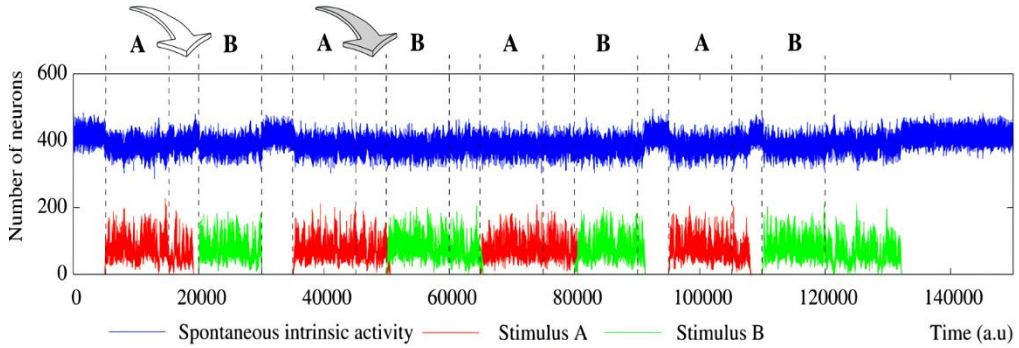

Figure 1.6 Evolution of the activity of a SW(10) short-term memory network that receives two stimuli in series. The network consists of 2500 neurons with the intraunit parameters shown in Table 1.5 Stimulus A is (1, 0, 1, 0, 1) and stimulus B (1, 1, 0, 1, 1). Labels on top indicate the stimulus injected in each stimulation episode. The figure plots the evolution of the spontaneous intrinsic activity (blue trace) and the emission level of the fingerprints associated to stimulus A (red trace) and B (green trace). In short-term memory networks, small differences resulting of the network topology exist on the network collective dynamics. If the stimulus detected in a prior episode survives in the network when a new stimulation episode starts, the new stimulus almost instantaneously wins the competition (winner-take-all competition) and the previous stimulus completely disappears from the network.

However, in-series stimulation induces new collective dynamics regarding the competition between stimuli A and B. In the case of equivalent short-term memory networks, no significant differences are found in their collective dynamics. As example of activity in these networks, Figure 1.6 depicts the activity of a representative short-term memory network with SW(10) topology that receives two stimuli in series. In many occasions, mainly in the most random networks, the activity evoked by a stimulus disappears from the network during the subsequent inter-stimulation interval. Then, when a new stimulation episode starts, the network has recovered a stable state with only spontaneous intrinsic activity and no competition between external stimuli occurs.

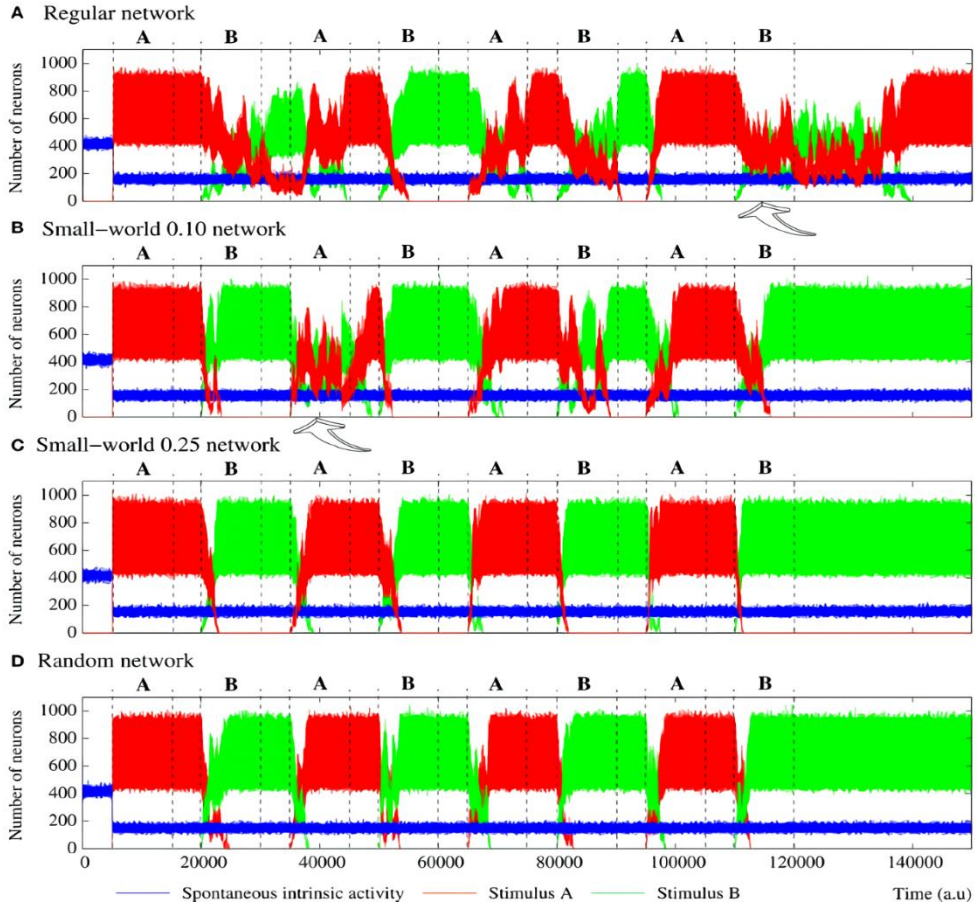

Figure 1.7. Equivalent figure to Figure 1.6, but for equivalent long-term memory networks with different topologies. These networks consist of 2500 units with the parameters shown in Table 1.5. Again, stimulus A is (1, 0, 1, 0, 1) and stimulus B (1, 1, 0, 1, 1). During the stimulation periods, a competition is established between stimuli A and B. In networks with a high degree of regular connections (A, B), this can be a winner-take-all or a winnerless competition. In the more random networks (C, D), it is always a winner-take-all competition where the activity supported by the corresponding active stimulus prevails.

This situation can be observed in different transition periods in Figure 1.6, for instance, in the pointed out by the white arrow. In other stimulation episodes, mainly in the more regular networks—where external stimuli reverberate for longer periods (see Section Network Memory)—a competition takes place between stimuli A and B. A priori, given the spatial organization of the patterns induced by stimuli in short-term memory networks with

a low level of activity (e.g., see Figure 1.4), we could expect that reverberating patterns encoding the stimuli transiently coexist within the network. Nevertheless, a fast-winner-take-all competition always occurs between both stimuli, and the last received stimulus quickly prevails over the other (e.g., transition period pointed out by the gray arrow in Figure 1.6). Once one of the external stimuli wins the competition, the number of neurons that recognize and emit the corresponding binary pattern fluctuates around a steady level. This steady level is nearly the same in all the stimulation episodes since neurons have the same permeability to stimulus A and B. Finally, when the stimulation ends, the last injected stimulus can reverberate in the network in the same way as in the single stimulus case.

More interesting results from the encoding point of view appear in the simulations of long-term memory networks receiving external stimuli in series (Figure 1.7). In these networks, once an external stimulus is detected, it persistently survives in the network. Therefore, given the stimulation protocol used in our simulations, a competition between the two incoming stimuli always happens when a new stimulation episode begins. Due to this competition, the time needed to reach a steady level in the number of neurons that follow each incoming stimulus is very variable in the different transition periods. Note also the difference in the transition of the collective activity as compared with the first stimulation episode where no competition between external stimuli is established ($p_r \gg p_e$). As we demonstrate in Section Detection of External Stimuli, the presence of random connections increases the level of activity induced by an external stimulus and the corresponding propagation velocity. When two stimuli are in series introduced into a random enough long-term memory network (e.g., a SW(25) network), this results in a relatively fast (as compared with networks with more regular topologies) winner-take-all competition where the activity supported by the active stimulus in each stimulation episode prevails. Thus, in networks with prevailing random connections, the last received stimulus always wins the competition and, therefore, the preferred pattern reverberating in the network starts following this stimulus (panels C, D of Figure 1.7). Conversely, the presence of regular connections benefits the competition between external stimuli (Section Detection of External Stimuli). Due to this phenomenon, it can be visually appreciated that when a winner-take-all competition among stimuli A and B takes place in more regular networks (see panels A, B of Figure 1.7), the last injected stimulus usually needs more time to win the competition than the required in the more random networks. Table 1.6 quantifies this result showing the mean time elapsed since the arrival of a new external stimulus until the binary pattern associated to the previous stimulus completely disappears from long-term memory networks with different topologies. In networks exhibiting winner-take-all competitions the arrival of a specific but minor stimulus in the network induces an alternation of activity in the whole ensemble.

Regular	SW(10)	SW(25)	Random
10.477.75 ± 4500.46	5759.95 ± 4376.25	3391.66 ± 1650.48	3226.42 ± 1.167.10

*The table shows the mean time that the long-term memory networks depicted in **Figure 1.7** need to "forget" a previously detected stimulus. This period is calculated from the beginning of a new stimulation episode to the instant where the level of activity related to the previous stimulus is equal to zero. Units are dimensionless. Mean data are calculated considering 20 simulations with different random seed, 5-bit stimuli introduced in the network, stimulated unit and connectivity. The higher the network regularity, the longer the competition period between external stimuli.*

Table 1.6. In long-term memory networks, stimuli survive in the network until a new stimulus arrives.

However, in the more regular networks, the mode of competition among external stimuli is not always a winner-take-all regime. As illustrated in the stimulation episodes pointed out by the arrows in panels A, B of Figure 1.7, transient winnerless competitions (Rabinovich *et al.*, 2001; Afraimovich *et al.*, 2004) can be established in these networks. Figure 1.8 shows a phase diagram depicting the regions where winner-take-all and winnerless competition regimes emerge in long-term memory networks of 2500 units with $p_e = 0.05$ as a function of the network topology as given by the rewiring probability parameter and the value of the intraunit parameter p_r. During winnerless regimes, no stimulus wins the competition and, therefore, both external stimuli coexist in the network although one of them is not supported by stimulation. Due to this competition dynamics, two interesting phenomena can be observed in the more regular long-term memory networks when the stimulation is over. On one hand, the persistently sustained stimulus is not necessarily the injected in the last stimulation episode. Panel A of Figure 1.7 shows an example of this effect. Although stimulus B arrives in the last stimulation episode, the stimulus that survives in the network after the end of the stimulation is stimulus A. On the other hand, a sustained winnerless competition between external stimuli can emerge in the network (this is illustrated above in Figure 1.13 for a network receiving nine external stimuli simultaneously). Therefore, these networks have the ability to behave as a long-term memory simultaneously encoding more than one stimulus.

The activity movies illustrating the evolving network dynamics give additional insight about the results derived from the level of activity analysis. When a new stimulation episode starts, the new stimulus induces the coexistence of different spatio-temporal patterns with different spatial organization. Figure 1.9 shows the evolving patterns generated by four representative examples of equivalent long-term memory networks during an inter-stimulation interval. The four sequences start just before the arrival of stimulus B, in a situation with a high level of synchrony in the network where the prevailing pattern corresponds to stimulus A (red points).

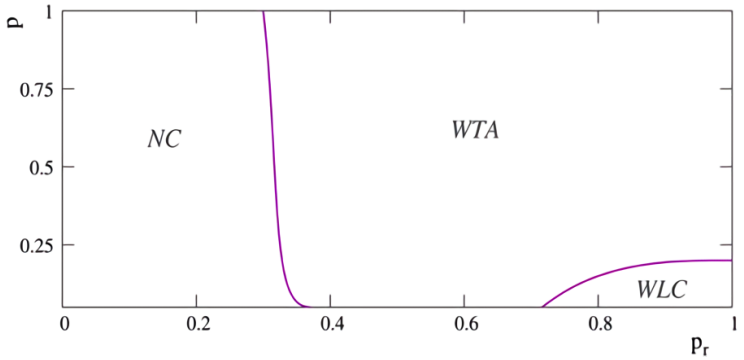

Figure 1.8 Phase diagram depicting the regions at which the different competition regimes emerge in networks of 2500 neurons with pe = 0.05. The x-axis corresponds to probability p_r and the y-axis to the rewiring probability parameter p, i.e., to the network topology. Note that p = 0 corresponds to regular networks and p = 1 to random networks. Label WLC denotes regions where transient winnerless competitions between external stimuli can appear in the network. Label WTA denotes regions where the mode of competition between external stimuli is always a winner-take-all regime. The region NC corresponds to networks where no competition among external stimuli takes place.

The arrival of stimulus B (second frame) produces new emerging spatio-temporal

patterns, and a competition among the two external stimuli starts. As Figure 1.7 shows, this competition depends on the network topology. Snapshots of Figure 1.9 can explain the transient winnerless competition dynamics observed in the more regular networks, and the winner-take-all dynamics in the more random ones. In the more regular networks (panels A, B of Figure 1.9), the evolving spatio-temporal patterns have a well-defined and coherent spatial structure. The clusterization and coherence of these transient patterns produce well-delimited boundary regions between stimuli A and B, which potentiates the competition. This improves the ability of the network to sustain multiple stimuli simultaneously. In the same way, the winner-take-all competition observed in the more random networks in Figure 1.7 is also observed in the snapshots of Figure 1.9. Note that the unstructured propagation of stimulus B makes it quickly replaces stimulus A within the network, reaching the typical fix spatial organization of the pattern.

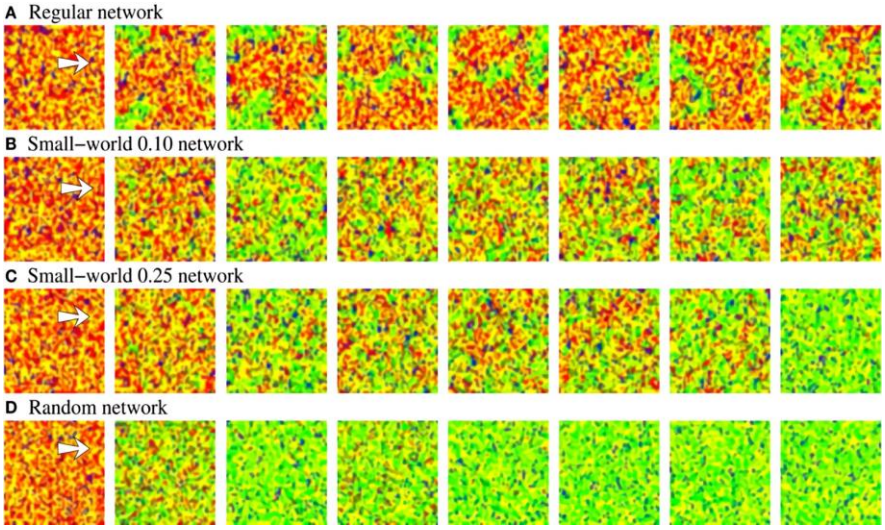

Figure 1.9 Snapshots of activity movies belonging to the networks depicted in Figure 1.7. The figure illustrates the evolving spatio-temporal patterns of activity observed in these networks as a function of the different modes of competition established between stimuli A and B when a new in-series stimulation episode starts. Sequences develop in time from left to right. To better appreciate the different evolving spatial structure of the patterns, the time interval between frames is different, but always the same in the four sequences. Neural activity is represented with a color code. Yellow corresponds to silent neurons, blue to the spontaneous intrinsic activity, red to stimulus A and green to stimulus B. The arrow in the first frame of each sequence points out the approximate location of the 2×5 stimulated cluster of neurons. When stimulus B arrives, it propagates through the network. Then, as the activity related to this stimulus grows, the activity related to stimulus A diminishes. When a winner-take-all competition occurs (C, D), stimulus B completely replaces to stimulus A. The higher the regularity of the network, the longer the transition period between stimuli. When a winnerless competition is established between stimuli A and B, both stimuli coexist in the network (A, B).

In-parallel stimulation

In the simulations where multiple external stimuli arrive in parallel to the network, we consider a single stimulation episode. During this time period, all the external stimuli considered in the experiment are simultaneously introduced in different groups of neurons. The set of neural fingerprints recognized by the neurons varies in the different experiments, but always consists of the serial binary patterns used as external stimuli during the corresponding stimulation period. Results are independent of the stimulation patterns and of

the location of the neurons that receive the external stimuli.

When stimuli are applied, they start to spread through the network and, again, new collective dynamics emerge in the network (Figures 1.10, 1.11). If we focus on the stimulation period, the same as in all the simulations described so far, on one hand, the spontaneous intrinsic activity (not shown in Figures 1.10, 1.11) drops due to the competition with the activity induced by incoming stimuli and, on the other hand, the total level of activity in the network reaches a steady level. However, as now multiple simultaneously active stimuli support their generation, coexisting patterns encoding the different external stimuli propagate through the network and compete between them. The same as in the in-series stimulation case (Section Encoding of Multiple Simultaneous Stimuli: In-Series Stimulation), the competition dynamics among the coexisting patterns of activity is the basis of the encoding of multiple stimuli. While the stimulation is present, now, it always arises a winnerless competition consisting of irregular intervals where the overall activity within the network is distributed in turn between the different external stimuli. In this sense, none of the stimuli neither prevails over the others nor reaches a steady emission level during the stimulation period. Depending on the connectivity, different winnerless regimes can arise in the network. Note that when the network is in-series stimulated, winnerless competition dynamics only arises in the more regular topologies. The activity movies illustrate the different spatial organization of the coexisting patterns of activity as a function of the network topology, which allows us to understand the different winnerless regimes. Snapshots of the evolution of the network activity of four equivalent long-term memory networks with different topologies are shown in Figure 1.12. When the network has a high degree of regular connections, coherent spatio-temporal patterns are formed due to the propagation of stimuli to close neighbors. In these networks, there are well-defined clusters of neurons that follow each stimulus and, therefore, it is established a winnerless competition where each external stimulus keeps a nearly constant level of activity. If one stimulus disappears from the network, new spatio-temporal patterns following it appear shortly after due to the stimulation.

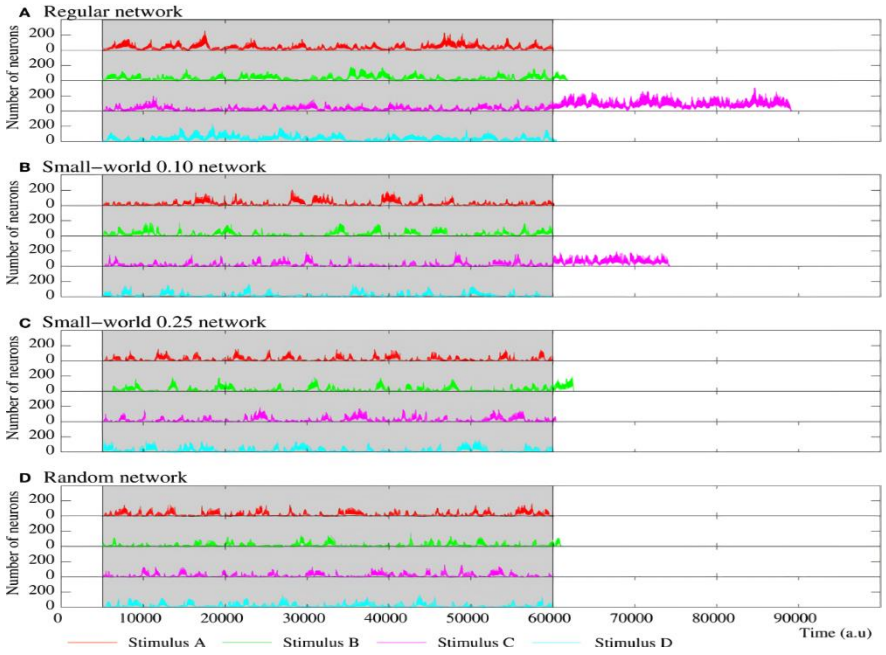

Figure 1.10 Evolution of the activity of four equivalent short-term memory networks receiving four stimuli in parallel. All of them consist of 2500 neurons with the parameters shown in Table 1.5. Stimulus A is (1, 0, 0, 0,

1), B (1, 0, 1, 0, 1), C (1, 1, 0, 1, 1), and D (1, 1, 1, 1, 1). The network collective dynamics is the same independently of the serial binary patterns used as external stimuli. The figure plots the number of neurons following each stimulus during and after the stimulation period (grayed area). Note that the spontaneous intrinsic activity is not shown. While the stimulation is present, a winnerless competition between the four stimuli arises within the network. When the stimulation ends, since they are not supported by an active stimulus, the binary patterns associated to the external stimuli disappear from the network after a reverberation period. As in all the previously discussed short-term memories, the more regular networks are able to sustain external stimuli for longer periods when the stimulation is over.

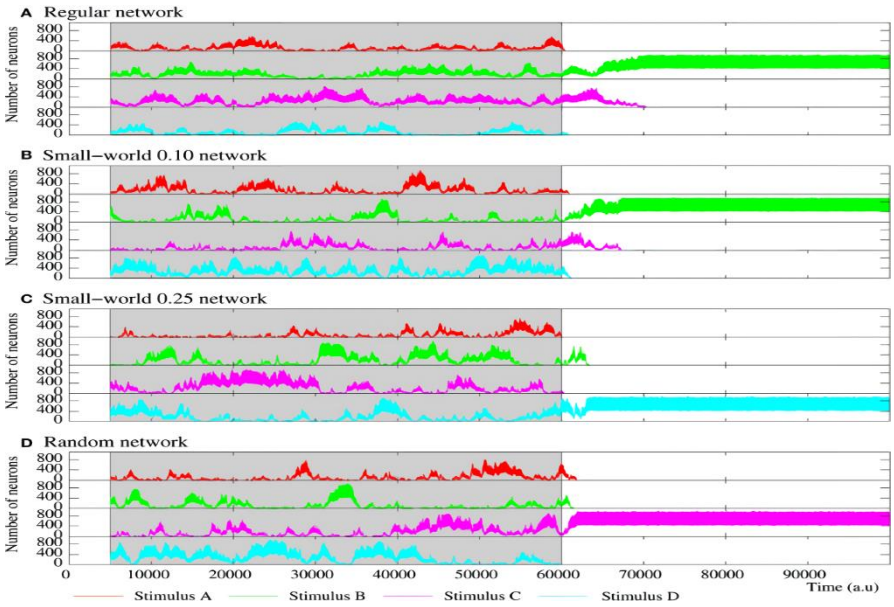

Figure 1.11. Figure equivalent to Figure 1.10, but for four representative examples of equivalent long-term memory networks of 2500 neurons with the intraunit parameters shown in Table 1.5. Stimulus A is (1, 0, 0, 0, 1), B (1, 0, 1, 0, 1), C (1, 1, 0, 1, 1), and D (1, 1, 1, 1, 1). During the stimulation period, a sustained winnerless competition emerges in the network. This consists of an irregular alternation of the level of activity related to each external stimulus. When the stimulation is over, at least a stimulus survives in the network.

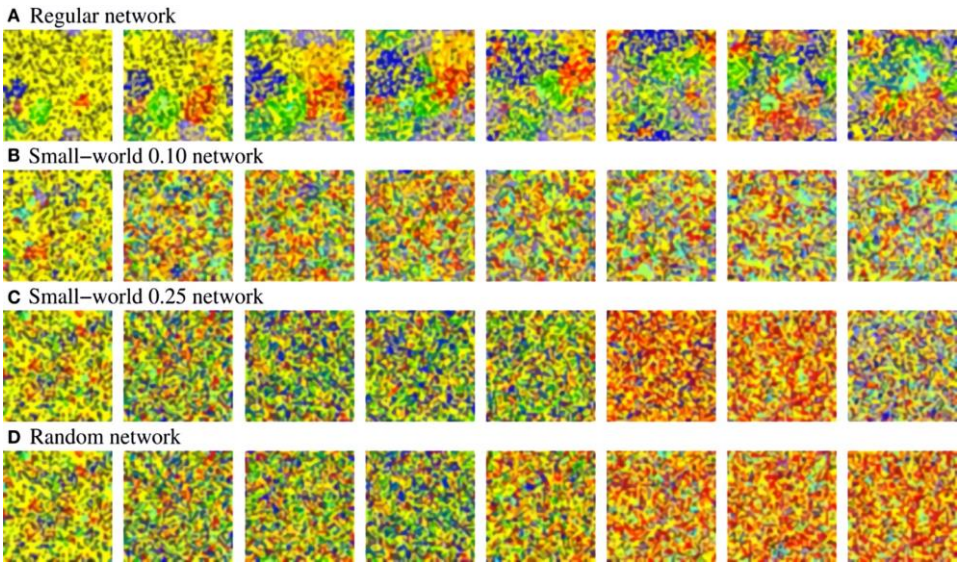

Figure 1.12. Snapshots of four representative activity movies of equivalent long-term memory networks with different network topologies receiving nine 9-bit stimuli in parallel. Similar patterns of activity are obtained in

short-term memory networks. Sequences develop in time from left to right. To better appreciate the spatial organization of the patterns, the time interval between frames in the sequence is variable, but always the same in the four sequences. Neural activity is represented with a color code. In this case, yellow corresponds to silent neurons or neurons emitting the spontaneous binary pattern. The rest of colors correspond to a different external stimulus. Note that we do not distinguish between silent neurons and neurons emitting the spontaneous pattern to simplify the graphical representation and better appreciate the evolution of the patterns. The figure shows the characteristic spatial organization of the patterns as a function of the network topology. In the more regular networks (A, B), several coherent spatio-temporal patterns coexist within the network. Conversely, in the more random networks (C, D), the number of coexisting patterns in a given time step is lower.

Regular	SW(10)	SW(25)	Random
7.77 ± 0.95	6.68 ± 1.18	4.51 ± 1.19	4.29 ± 1.11

We consider that the network encodes a stimulus when the number of neurons that follow it is greater than ten (i.e., the number of stimulated cells). Mean data are calculated considering 20 different simulations with different random seed, external stimuli introduced in the network and connectivity.

Table 1.7 Mean number of stimuli encoded during the stimulation period in the networks shown in Figure 1.12 when they receive nine simultaneous 9-bit stimuli.

Conversely, in networks with a high level of random connections, the presence of connections between distant neurons produces patterns of activity with a lower spatial structure and a faster propagation velocity. These two features induce a competition between the stimuli induced activity that makes a few stimuli (in the examples of Figures 1.10, 1.11, only one or two) transiently prevail over the others. This translates into a winnerless competition regime consisting of the alternation of irregular cycles where the preferred pattern in the network follows different stimuli. Note how in the snapshots of panels C, D in Figure 1.12, the prevailing colors in each frame change as time evolves, while in panels A, B the color distribution is homogeneous. The lower the randomness, the higher the number of coexisting spatio-temporal patterns within the network. Therefore, connections to close neighbors increase the ability of the network to sustain multiple incoming stimuli simultaneously. Table 1.7 corroborates this result by calculating the mean number of coexisting stimuli in equivalent long-term memory networks during an in-parallel stimulation where nine stimuli are simultaneously applied.

Finally, results observed in short-term memory networks when the stimulation is over are equivalent to those obtained during in-series stimulation. In long-term memory networks, a winner-take-all competition usually occurs and the reverberating patterns follow one of the external stimuli (Figure 1.11). Nevertheless, in some simulations of regular long-term memory networks a sustained winnerless competition between two or three stimuli is established in the network beyond the stimulation period. Figure 1.13 illustrates this encoding mechanism in a long-term memory network that receives nine different stimuli. This result emphasizes the increasing ability to encode multiple simultaneous stimuli that the presence of regular connections provides to the neural network.

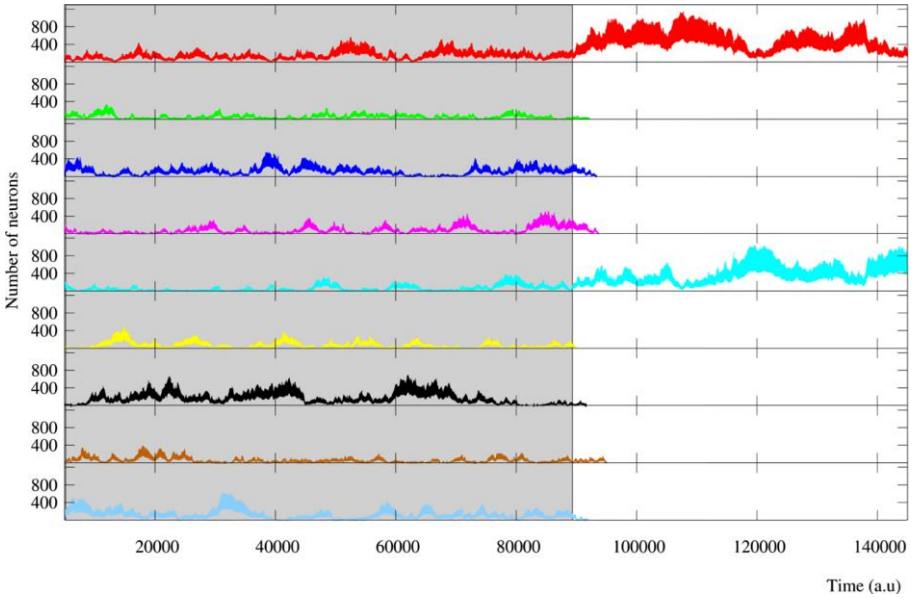

Figure 1.13. Evolution of the activity of a regular long-term memory network where nine external stimuli are injected in parallel. Each trace corresponds to a different external stimulus using the same color code as in Figure 1.12. Grayed area identifies the stimulation period. This figure illustrates how connections to close neighbors promote the competition between the activity induced by the different external stimuli. This implies that these networks are able to encode a larger number of stimuli simultaneously, even after the stimulation period when they are not supported by an active stimulus.

DISCUSSION

The idea that neural systems can encode information in the precise timing of spikes has attracted increasing attention over the last years. The presence of precise firing patterns in different neurons has been reported in several vertebrate and invertebrate neural circuits (Elson *et al.*, 1999; Reinagel and Reid, 2000, 2002; Chi and Margoliash, 2001; Hunter and Milton, 2003). Experimental evidence demonstrates that some of these precise temporal structures allow the discrimination of neural signals. For instance, the bursting activity of some neurons belonging to very different animals displays intraburst neural signatures in the form of cell-specific interspike interval distributions (Szücs *et al.*, 2003; Szücs *et al.*, 2005; Garcia *et al.*, 2005; Campos *et al.*, 2007; Zeck and Masland, 2007). Similarly, some neural systems can display specific firing patterns associated to behavioral or functional states (Klausberger *et al.*, 2003; Somogyi and Klausberger, 2005; Kaping *et al.*, 2011). However, although there is an increasing amount of new results on the strategies of information processing used by neural systems (VanRullen *et al.*, 2005; Rabinovich *et al.*, 2006; Kumar *et al.*, 2010), the existence of characteristic features in an individual neural signal allowing a reader to discriminate its inputs has not been investigated in great detail. This kind of information processing can be a powerful strategy for neural coding. Model simulations support the hypothesis that intraburst neural signatures could be part of a multiplexed code where the neuron identity could be transmitted together with the circumstantial message (Latorre et al., 2006, 2007). Readers of these signals can take advantage of these multiple simultaneous codes and process them one by one or simultaneously to perform different tasks (Latorre *et al.*, 2006; Baroni *et al.*, 2010). Thus, if a neural system is able to recognize different neural fingerprints in its input signals and adjust its behavior to them, it could discriminate or contextualize their inputs as a function of general aspect of the signal like specific interspike frequencies via resonance (Izhikevich *et al.*, 2003),

but also as a function of a specific emitter or task. This is a very desirable ability in multifunctional systems.

This work presents a simulation study showing that a simple neural network model composed of neurons that are able to emit and recognize neural fingerprints can detect specific patterns in its input signals and encode these stimuli in its collective dynamics. The processing and encoding ability of the network is related to the competition established between the spontaneous intrinsic activity and/or the activity evoked by the arrival of external stimuli. This competition may change from winner-take-all to winnerless regimes. When the level of spontaneous intrinsic activity is too high, this wins the competition and external stimuli do not propagate through the network, which avoids the generation of spatio-temporal patterns. This provides a "reset" mechanism to the network. Only by increasing the level of spontaneous intrinsic activity, the network stops processing and the previously detected stimuli almost instantaneously disappear from the network. The coexistence of stimuli in the network is related to the different clusterization and coherence of the transient spatio-temporal activity generated in response to external input. When a winner-take-all competition occurs between the spatio-temporal patterns of activity evoked by different stimuli, one stimulus prevails over the others and only its corresponding patterns travel through the network (globally or locally). On the other hand, when a winnerless competition emerges in the network, the total encoding capacity of the network is alternately distributed among different stimuli. The main factors governing the mode of competition are the level of spontaneous activity and the permeability to external stimuli. Both are driven by intraunit parameters (p_e and p_r, respectively). However, changes in the collective dynamics are also observed as a function of the network topology. The presence of random connections has a similar effect to increase the permeability to external stimuli. These connections facilitate the detection of specific external stimulus in the sense that they increase the stimulus propagation velocity and the level of activity related to stimuli. Networks with a more regular topology (connections with close neighbors) usually benefit the competition between external stimuli. This implies that these networks are able to encode a larger number of stimuli simultaneously.

When the stimulation is over, the same competition regimes emerge between the coexisting spatio-temporal patterns following external stimuli. The only difference is that, now, these patterns are not supported by stimulation and, therefore, when a stimulus loses the competition with other stimuli or with the spontaneous intrinsic activity, it completely disappears from the network. In this way, the patterns of activity induced by external stimuli can almost instantaneously disappear from the network when the stimulation is over. This can be a desirable behavior for some systems. However, the more interesting situations are those where the network displays short-term or long-term memory abilities. In short-term memory networks the stimulus induced activity transiently reverberate within the network. Conversely, in long-term memory networks, the stimuli lead the network to a new stable state where the reverberating patterns related to stimuli becomes a network effect. Then, the stimulus persistently survives in the network until a new stimulus arrives. A short-term memory can become a long-term memory only by increasing the neurons' permeability to external stimuli, and vice versa. In the same way, increasing the number of connections to close neighbors benefits short-term memory mechanisms; while increasing the presence of random connections potentiates the long-term memory mechanisms.

The results reported in this paper indicate that information processing based on the identification of specific neural fingerprints can be a plausible and flexible strategy for neural

systems. Different complex dynamic regimes are observed in a simple network of neurons that communicate by exchange of neural fingerprints. Intraunit parameters affecting the individual information processing and the network topology can tune the self-organizing properties of the network. This indicates the great adaptability of the network to different modes of operation and, although not addressed in this paper, the large flexibility to implement both synaptic and subcellular plasticity (Davis, 2006). These results call for more realistic models for the activity of individual neurons, which can introduce a higher information processing capacity in the network.

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Capítulo 2

Implementación de redes basadas en firmas neuronales con neuronas spiking

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RESUMEN

Las redes neuronales spiking son el enfoque más prometedor para desarrollar redes neuronales artificiales (RNA) realistas. A diferencia de los paradigmas más tradicionales basados en el ratio de disparo, la codificación de información en las redes spiking se basa en el tiempo preciso en que se produce cada potencial de acción. Se ha demostrado que redes neuronales artificiales de tipo spiking pueden aplicarse satisfactoria y eficientemente en múltiples problemas realistas, como la clasificación o el reconocimiento de patrones, en los que tradicionalmente se han utilizado redes neuronales basadas en otro tipo de estrategia. En los últimos años, los avances en el campo de la Neurociencia han permitido describir nuevos principios computacionales en diferentes sistemas neuronales vivos. ¿Podrían las RNA beneficiarse de algunos de estos descubrimientos que proporcionan nuevos elementos de inspiración? Ésta es una pregunta muy interesante para la comunidad científica, por lo que el desarrollo de redes spiking que incluyen nuevas estrategias de codificación y procesamiento de información bioinspirada está recibiendo una gran atención en los últimos años. Desde esta perspectiva, en este trabajo, adaptamos para su uso en una red neuronal spiking los conceptos fundamentales de un paradigma de red neuronal basado en firmas (*Signature Neural Networks*) que se ha propuesto recientemente. En concreto, hacemos uso de firmas neuronales individuales para identificar cada unidad de la red, hay una contextualización local de la información durante el procesamiento y se utilizan estrategias de codificación multicódigo relativas al origen y el contenido del mensaje para la propagación de la información. Ninguno de estos mecanismos se ha utilizado todavía en el contexto de las RNA spiking. Nuestra investigación proporciona una prueba de concepto de su aplicabilidad en dichas redes. Las simulaciones muestran que un modelo simple de red como el que aquí discutimos exhibe propiedades complejas de auto-organización. La combinación de múltiples esquemas de codificación simultánea permite a la red generar patrones de actividad espacio-temporales coexistentes que codifican la información en diferentes dimensiones espacio-temporales. En función de los parámetros de la red y/o de los parámetros que definen la modalidad de codificación correspondiente dentro de cada unidad individual, pueden surgir diferentes formas de competición entre los patrones evocados en la red incluso en ausencia de conexiones inhibitorias. Estos parámetros también modulan la capacidad de "memoria" de la red. Los comportamientos dinámicos observados en las diferentes dimensiones de información en un momento dado son independientes y sólo dependen de los parámetros que configuran el tratamiento de la información en esa dimensión. En vista de estos resultados, argumentamos que la existencia de mecanismos de plasticidad dentro de cada neurona individual y las estrategias de codificación multicódigo pueden proporcionar propiedades computacionales

adicionales a las redes neuronales spiking, lo que podría mejorar su capacidad y rendimiento en una amplia variedad de tareas del mundo real.

IMPLEMENTING SIGNATURE NEURAL NETWORKS WITH SPIKING NEURONS

Abstract Spiking Neural Networks constitute the most promising approach to develop realistic Artificial Neural Networks (ANNs). Unlike traditional firing rate-based paradigms, information coding in spiking models is based on the precise timing of individual spikes. It has been demonstrated that spiking ANNs can be successfully and efficiently applied to multiple realistic problems solvable with traditional strategies (e.g., data classification or pattern recognition). In recent years, major breakthroughs in neuroscience research have discovered new relevant computational principles in different living neural systems. Could ANNs benefit from some of these recent findings providing novel elements of inspiration? This is an intriguing question for the research community and the development of spiking ANNs including novel bio-inspired information coding and processing strategies is gaining attention. From this perspective, in this work, we adapt the core concepts of the recently proposed Signature Neural Network paradigm—i.e., neural signatures to identify each unit in the network, local information contextualization during the processing, and multicoding strategies for information propagation regarding the origin and the content of the data—to be employed in a spiking neural network. To the best of our knowledge, none of these mechanisms have been used yet in the context of ANNs of spiking neurons. This paper provides a proof-of-concept for their applicability in such networks. Computer simulations show that a simple network model like the discussed here exhibits complex self-organizing properties. The combination of multiple simultaneous encoding schemes allows the network to generate coexisting spatio-temporal patterns of activity encoding information in different spatio-temporal spaces. As a function of the network and/or intra-unit parameters shaping the corresponding encoding modality, different forms of competition among the evoked patterns can emerge even in the absence of inhibitory connections. These parameters also modulate the memory capabilities of the network. The dynamical modes observed in the different informational dimensions in a given moment are independent and they only depend on the parameters shaping the information processing in this dimension. In view of these results, we argue that plasticity mechanisms inside individual cells and multicoding strategies can provide additional computational properties to spiking neural networks, which could enhance their capacity and performance in a wide variety of real-world tasks.

Keywords bioinspired ANNs · Neural signatures, subcellular plasticity · Multicoding · Local contextualization · Signature neural network · Spiking neuron

Biological neural circuits are powerful computational systems that efficiently process a great amount of data in real time with extensive plasticity capabilities. This makes the nervous system a source of inspiration when designing engineered tools. In this sense, many Artificial Neural Network (ANN) paradigms mimicking the computational principles performed by living neural systems have been developed to solve real-world problems (Michie et al., 1994; Bishop, 1995). Nevertheless, the bio-inspiration in most cases is limited to a knowledge about neural information processing that was available more than 60 years ago. A challenge in ANN research is related to incorporate novel bio-inspired information coding and processing strategies to the network design since they can contribute to enhance the network capacity to perform a given task (Rumbell *et al.*, 2014).

Information coding in the nervous system is mainly based on the generation, propagation, and processing of action potentials or spikes (Bialek *et al.*, 1991; Kandel *et al.*, 1991; Rieke *et al.*, 1999). Most of the neural computation is driven by these events. The classical view of neural coding emphasizes the importance of information carried by the rate at which neurons discharge action potentials. However, experimental evidence indicates that living neural

systems use many different information coding strategies (Rabinovich *et al.*, 2006b; Middleton *et al.*, 2011), which greatly enhances their processing capacity as compared to the classical view. In this scenario, temporal coding emerges as a strategy commonly used by neural systems, emphasizing that, unlike (or in addition to) the firing rate paradigm, neural information may be carried by precise individual spike timings (e.g., see Mainen and Sejnowski, 1995; Lestienne, 1996; Diesmann *et al.*, 1999; Reinagel and Reid, 2002).

Traditional ANN paradigms are mostly based on highly simplified information processing mechanisms derived from the neural coding classical view. However, the growing experimental evidence of the importance of temporal code to explain neural computation gave rise to the Spiking Neural Networks, nowadays considered the third generation of ANNs (Gerstner, 1995; Maass, 1997b). In the two previous generations, neuron models employ threshold gates and activation functions, such as sigmoid functions, to propagate analog values to their neighbors. In contrast, spiking neurons communicate and encode information using discrete spikes (Gerstner *et al.*, 1993; Deco and Schürmann, 1998; Maass and Bishop, 2001; Gerstner and Kistler, 2002; Bohte, 2004; Brette *et al.*, 2007; Ponulak and Kasinski, 2011). This allows spiking neural networks to solve computational tasks using a firing-rate based strategy as their analog counterparts (O'Connor *et al.*, 2013; Diehl *et al.*, 2015; Esser *et al.*, 2016), but discrete spiking activity provides additional dimensions for information coding (e.g., time, frequency or phase), which makes ANN of spiking neurons a promising approach for solving complex computational tasks. Theoretical efforts try to illustrate that computing and modeling with these networks may be biologically plausible and computationally efficient (Maass, 1997a; Izhikevich, 2004; VanRullen *et al.*, 2005; Cessac *et al.*, 2010). It has been shown that spiking neural networks are at least as computationally powerful as traditional ANN paradigms (Maass, 1996, 1997a; Natschläger and Ruf, 1998; Ruf and Schmitt, 1998). In applied engineering, spiking ANNs have been successfully used in different practical applications, such as motor control, odor recognition, image classification, or spatial navigation between others (see Ponulak and Kasinski, 2011, for an overview).

Although they are closer to their biological counterparts, most ANN paradigms of spiking neurons do not include relevant computational principles experimentally and theoretically studied in the nervous system. For instance, most neuro-inspired paradigms consider network elements as indistinguishable units; they only implement synaptic learning based on adjusting the synaptic weights (Bohte *et al.*, 2002b; Kube *et al.*, 2008; Ponulak and Kasinski, 2011); and individual units are considered integrators that integrate synaptic input over time until a given threshold is reached. Experimental evidence demonstrates that neural computation does not only include synaptic integration and synaptic plasticity, but also subcellular plasticity, i.e., intra-unit mechanisms that allow a neuron to tune its intrinsic dynamics and shape the computation of its output response as a function of the incoming information (Zhang and Linden, 2003; Turrigiano and Nelson, 2004; Davis, 2006; Turrigiano, 2007). Likewise, it is commonly considered that the information arriving to a neuron is encoded through a single code, e.g., the rate or the precise timing of spikes, when the need for several simultaneous codes (multicoding) in the nervous system seems to be apparent (Latorre *et al.*, 2006; Kayser *et al.*, 2009; Panzeri *et al.*, 2010). Living cells receive many inputs from different sources and send their output to different neurons too. An effective way to improve communications is combining multiple encoding modalities in the same signal. Not all the readers have to be interested in the same modality at the same time, specially when we talk about multifunctional networks. This kind of information processing requires of local information discrimination /

contextualization mechanisms that allow a neuron to process the multiple simultaneous codes in its input signals one by one or simultaneously in order to perform different tasks. Subcellular plasticity emerges as a highly relevant strategy to perform this context-dependent information processing.

Signature Neural Networks represent a novel self-organizing bio-inspired ANN paradigm that incorporates some of these concepts (Latorre *et al.*, 2011). Behind this ANN paradigm, there are three main ideas. (1) Each neuron of the network has a signature that allows its unequivocal identification by the rest of the cells. (2) The neuron outputs are signed with the neural signature. Therefore, there are multiple codes in a message regarding the origin and the content of the information. (3) The single neuron discriminates the incoming information and performs a distinct processing as a function of the multiple codes in the network. Nevertheless, in spite of being inspired in a precise temporal structure, signature neural networks are non-spiking ANN. The main goal of this work is to assess whether the information coding and processing strategies proposed by the signature neural network paradigm are plausible for spiking networks. With this aim, we morph the core concepts of the existing non-spiking paradigm to build an ANN of spiking neurons.

Bursting activity consists of series of high-frequency spikes that alternate with quiescent periods with only subthreshold activity (Izhikevich, 2006). This is particularly suitable to implement multicoding, since it involves the presence of at least two different time scales that can serve to encode distinct informational aspects. It has been also suggested that the burst length or the number of spikes in a burst can be used by living neurons to encode information (Kepecs and Lisman, 2003, 2004). Information can also be encoded in the intraburst firing pattern. In the bursting activity of the leech heartbeat control circuit, the temporal structure of the first spikes in the burst allows predicting the length and number of spikes of the burst (Campos *et al.*, 2007). Another relevant temporal structure within the burst is the intraburst neural signature, in which the signature neural network paradigm is inspired. Intraburst neural signatures are very precise and cell-specific spike timings experimentally observed in the bursting activity of cells of different vertebrates and invertebrates living neural circuits (Szücs *et al.*, 2003; Szücs *et al.*, 2005; Garcia *et al.*, 2005; Zeck and Masland, 2007; Brochini *et al.*, 2011). In central pattern generators (CPGs), they depend on the synaptic organization of the network (Latorre *et al.*, 2002; Rodríguez *et al.*, 2002; Szücs *et al.*, 2003). These precise temporal structures coexist in the neural signals with relevant information encoded with other encoding modalities. Their possible functional meaning for the neurons that belong to the same or to other neural system is still an open question. Model simulations of CPG circuits (Latorre *et al.*, 2004, 2006, 2007) point out that they can have important implications for the understanding of the origin of the CPG rhythms, the fast and fine tuning to modulation and the signaling mechanisms to other interconnected systems (other CPGs or muscles that the CPG controls). These modeling results have shown that cell-specific intraburst spike timing can be part of a multicoding strategy of bursting neurons. The readers of these signals may be able to read these characteristic firing patterns to perform different tasks in response to the multifunctional signals from each CPG cell.

In the context of ANN, bursting activity has been labeled as a "non-standard" behavior (Kampakis, 2013). However, taking into account the previous considerations, the individual units of the proposed network have bursting behavior. We argue that the additional dimensions to encode information provided by bursting activity can significantly increase the computational power of a spiking network. In particular, here we consider two encoding

schemes in the bursting signals: a rhythmic encoding modality, in which information is carried by the bursting frequency; and a spike-timing encoding modality; in which information is carried by specific intraburst spike patterns. Each individual neuron has a characteristic intraburst neural signature that uses to sign its output signals in the spike-timing encoding dimension. Finally, the model incorporates intra-unit history-dependent processing rules to compute the response in the spike-timing encoding dimension as a function of previous incoming signals. This local contextualization mechanism can be considered a particular case of subcellular plasticity. The idea behind this network design is transforming different stimuli and/or different relevant aspects of the inputs into different coexisting spatio-temporal spaces that encode information in a distributed network form.

The analysis of the emerging collective dynamics and the self-organizing properties of the network discussed in this paper points out that novel bio-inspired processing strategies could enhance the spiking ANNs capacity and performance. In particular, we provide a proof-of-concept that combining multiple encoding modalities in the network allows transforming incoming data into different spatio-temporal spaces, from which different aspects of the data, including their source, could be exploited one by one or globally. Different collective processing strategies can be implemented in each information dimension only by tuning the synaptic or intra-unit parameters, which facilitates parallelism and multifunctionality in the network. All these features would potentially increase the computational power of spiking ANNs and their ability to model complex high-dimensional processes.

METHODS

Network Model

Signature neural networks use neural fingerprints to identify each individual unit of the ensemble (Latorre *et al.*, 2011). For the spiking network proposed here, we take inspiration from the CPG circuits and use interspike interval signatures to achieve this feature. Thus, the fingerprint of a neuron (n_i) is a cell-specific intraburst spike timing distribution described as the sequence $S_i = \{ISI_1, ISI_2, \ldots, ISI_n\}$, where ISI_n represents interspike intervals between consecutive spikes within the same burst. The timing of the last spikes in the bursting activity of the pyloric CPG cells varies from one burst to another; while the first spikes in the burst are highly reliable (Elson *et al.*, 1999; Varona *et al.*, 2001a, b) and contain the neural signature (Szücs *et al.*, 2003; Szücs *et al.*, 2005). Mimicking this behavior, we consider two parts in a burst. The first part is used to sign the output messages and contains the signature of the emitter neuron (S_i). The spike timings of the second part of the burst are given by a preferred output pattern ($P_i = \{t_0 = 0, t_0, t_2, \ldots, t_N\}$) that changes dynamically as a result of the single neuron plasticity (see Section Intra-UnitPlasticity).

Spiking-bursting activity allows the simultaneous propagation of different units of information throughout the network (multicoding). Therefore, different spatio-temporal spaces can be simultaneously used to globally encode and store information. In the network discussed in this paper, we consider two coexisting units of information in each neural signal: the bursting frequency and the neural fingerprints included within the burst. In the first dimension, the network must generate and coordinate spatio-temporal patterns of propagating transient bursting activity (rhythmic encoding modality). To achieve this, we impose two

constraints (Wiedemann and Lüthi, 2003; Tabak *et al.*, 2010): (i) predominance of excitatory synapses and (ii) a refractory period in each neuron following hyperexcitation. Information processing in the second dimension is based on the emission and recognition of specific neural signatures (Tristán *et al.*, 2004; Carrillo-Medina and Latorre, 2015), i.e., information in this dimension propagates encoded in a spike-timing modality. An intra-unit contextualization mechanism drives the signature emission and recognition processes. This does not only allow us to illustrate a novel information processing strategy in the context of spiking neural networks, but also the dynamical richness that subcellular plasticity can provide to these networks.

Neuron Spontaneous Dynamics

Many spiking models generate output bursts depending on the parameter settings and/or the input stimuli (e.g., the models by Hindmarsh and Rose, 1984, Komendantov and Kononenko, 1996, or Liu *et al.*, 1998) that we have previously used to investigate the functional meaning of neural signatures). However, simulations show that the neural signatures in these models mainly depends on the network connectivity (Latorre *et al.*, 2002) and, to our knowledge, none of the existing spiking models displays an adaptive fingerprint as required by our study. A possible alternative to this issue is using the mechanism described in Marin et al. (2014) to tune neuron busting models and produce neural signatures equivalent to those observed in living cells. However, the generation of realistic signatures is out of the scope of this proof-of-concept.

To describe the individual behavior of each unit, we define a stochastic model operating in a discrete event framework. The neuron activity is considered as a discrete variable and characterized in time by V(t), its "membrane potential." Figure 2A illustrates schematically the neuron spontaneous dynamics. Our model neuron integrates and processes the information received through its different input channels (synaptic integration), adapts its firing pattern to the incoming information (intra-unit plasticity), and generates a coherent signed output signal. During subthreshold activity, the spontaneous evolution of the neuron activity is determined by the probability p—the transit probability of the internal state per time step. When the membrane potential of a neuron n_i reaches the firing threshold (TH), this generates a sequence of spikes (not a single spike). The temporal distribution of spikes within the response burst is given by a firing sequence composed of concatenating the signature (S_i) and the preferred output spike pattern (P_i) of the neuron. Then, the stochastic dynamics of a single neuron depends on the temporal evolution of the neuron activity and whether it is under (subthreshold activity) or over (spiking-bursting activity) the firing threshold. Formally:

- During subthreshold activity ($V_i(t) < TH$):

$$V_i(t+1) = \begin{cases} V_i(t) + I_{syn} + 1 & with\ probability\ p \\ V_i(t) + I_{syn} & otherwise \end{cases} \quad (1)$$

  where I_{syn} is the synaptic input (Equation 3) and p the transit probability of the internal state per time step.

- During the generation of the burst ($V_i(t) >= TH$):

$$V_i(t+1)= \begin{cases} AP & If\ t = t_1 + t_n \\ TH + 1 & If\ t = t_1 + t_n + 1, \quad \forall \neq N \\ 0 & If\ t = t_1 + t_N + 1 \\ V_i(t) + 1 & \text{otherwise with probability } p \\ V_i(t) & \text{otherwise} \end{cases} \quad (2)$$

where N is the number of spikes in the firing sequence ($S_i + P_i$), t_n denotes the timing of the nth spike in this sequence, (i.e., t_1 corresponds to the initial timing of the burst) and being AP the peak membrane potential to generate a spike. Note, that during the burst generation synaptic input (I_{syn}) is not taken into account (cf. Equation 1 and 2). After generating a burst, neurons have a refractory period of RP time steps during which $V_i(t) = 0$. Then, subthreshold dynamics starts again.

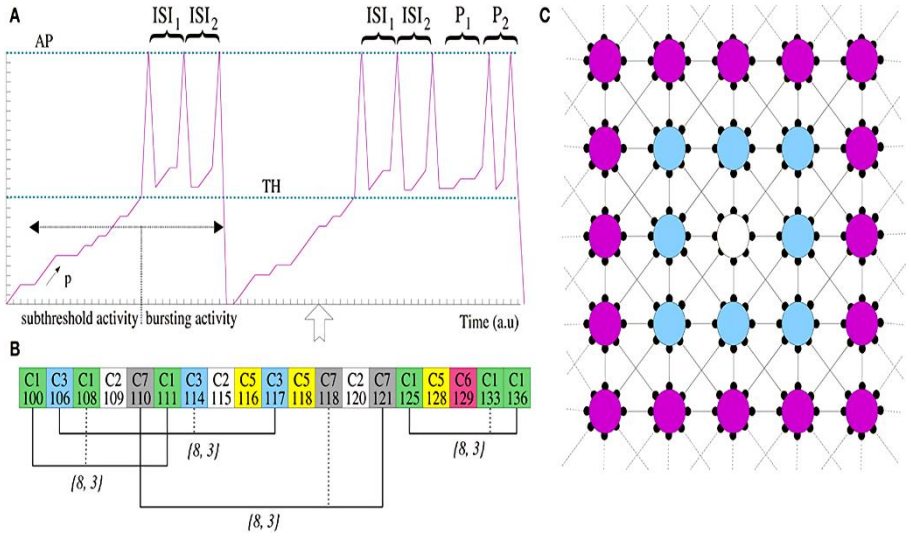

Figure 2.1. (A) Schematic representation of the stochastic neuron model (see main text for details). S={ISI_1, ISI_2} and P = {P_1, P_2} denote the neuron signature and the preferred output pattern, respectively. Note that the intraburst firing pattern is different in the first and the second burst. This is because, as (B) illustrates, the neuron recognizes a signature at the time step pointed by the arrow and intra-unit plasticity changes the neuron response in the spike-timing encoding modality. (B) Example of signature recognition. For each incoming spike, the local informational context keeps track of the corresponding input channel and spike timing (e.g., $C_{1\text{-}100}$ means that at time step 100 a spikes arrived to the neuron through channel C_1). This transient memory provides an intra-unit contextualization mechanism to the single neuron. For example, if the arrow in (A) corresponds to time step 136 and an input spike arrives through channel C_1, the neuron can contextualize this spike and determine that the signature {8, 3} have been received four times in the recent history. If this value is greater than the learning threshold (L_i), the neuron recognizes this signature and, consequently, modulates its output firing pattern as illustrated in the second burst of (A). (C) Network topology. Each neuron is directly connected to its eight nearest neighbors with periodic boundary conditions. Then, neighbors of the white unit are the blue neurons.

Synaptic Input

Synaptic input arrives to a neuron through two kind of input channels: connections with other neurons and an external channel to introduce external stimulation into the network. Each neuron in the network is connected to its eight nearest neighbors (Figure 2.1C) with periodic

boundary conditions. As in every spiking neural network, neurons communicate with each other through the generation and propagation of spikes. Then, the interchange rule is defined by:

$$I_{syn} = g_e \bullet pulse_e + \sum_j g_{ji} \cdot pulse_j \quad (3)$$

where g_e defines the weight of the external stimulus, $pulse_e$ is 1 when an action potential is delivered through the external channel and 0 otherwise; and, similarly, g_{ji} is the weight of the connection between neurons n_j and n_i and $pulse_j$ is 1 when $V_j(t-1)$ = AP and 0 otherwise. Note that Equation 3 does not apply neither during the generation of a burst (Equation 2) nor during the refractory period, i.e., in these situations synaptic input is not considered.

It is important to highlight that in this paper we do not discuss synaptic learning (see Section Discussion). This implies that g_{ji} is constant for all the synapses and, consequently, the neighborhood of every neuron does not change.

Intra-Unit Plasticity

Incorporating subcellular plasticity to a neuron model implies that a mechanism inside the cell allows tuning the neuron dynamics to incoming signals and/or to particular processing states. We consider here a history-dependent contextualization mechanism driving the spike-timing encoding modality. This intra-unit contextualization modulates the preferred output pattern as a function of previous incoming spike patterns.

As in the non-spiking signature neural network paradigm, to implement local contextualization, each individual neuron uses a transient memory, called local informational context. The local informational context keeps track of the information received during a time window of M_i time units, providing a history-dependent contextualization mechanism to the single neuron processing. In the case of our spiking network, for each incoming spike, the neuron stores in its local context the joint information about the input channel and the spike timing (Figure 2.2B). In this way, different intra-unit plasticity rules can be defined to take into consideration the input spike timings. In particular, the following rule can be used to recognize specific neural signatures:

- when a spike arrives to a target unit, this check whether the spike pattern received though the corresponding input channel appears in its local informational context so many times as a given learning threshold, L_i. If so, the receptor recognizes this fingerprint, which implies that the preferred output pattern is overwritten with the recognized fingerprint.

Figures 2.1A, B illustrate how intra-unit plasticity tunes the output firing pattern in response to the fingerprint recognition. During the generation of the first burst in the time series, the neuron does not recognize any signature. Therefore, there is not a preferred output pattern and the burst only contains the signature of the neuron ($S = \{ISI_1, ISI_2\}$). At time step 136 (pointed by the arrow), a spike arrives through channel C_1. The neuron can use its local informational context (Figure 2.1B) to contextualize this spike. In our case, this means to identify the incoming pattern through this channel (in this case {8, 3}) and to determine that this fingerprint has been received four times from time step 100. Then, assuming that the

learning threshold is L_i = 4, the neuron's preferred output spike pattern changes due to the recognition of the signature S' = {8, 3}. As a consequence, the intraburst firing pattern of the second burst in the time series varies to encode additional information (in the example, the sequence $P = \{P_1 = 8,\ P_2 = 3\}$). The neuron emits the new preferred output pattern until a new fingerprint is recognized or until the recognized fingerprint appears less than L_i times in the local informational context (keep in mind that this is transient memory). Note, that intra-unit plasticity can be used to compute different aspect of the output signal as a function of the local contextualization, not only the spiking firing pattern. For instance, a particular cell could increase/decrease its level of activity or generate an output spike in response to specific incoming patterns independently of the synaptic weight.

During the input processing, channels are checked randomly in each iteration. In this way, when the target neuron recognizes multiple signatures in the same iteration, the last processed prevails over the others. Plasticity rule does not apply during the generation of a burst—i.e., once the neuron starts firing, the output spike pattern cannot change.

Analysis Methods

Rhythmic Encoding Modality

To illustrate the spatio-temporal patterns generated in the bursting informational dimension, we generate activity movies representing the membrane potential evolving dynamics. In these movies, the evolution in time of the activity of a given unit ($V_i(t)$) is represented with a color scale. Regions with the same color have synchronous behavior. Red corresponds to neurons with a membrane potential over the firing threshold ($V_i(t) > TH$), i.e., they are generating a burst. Intermediate colors between blue and red, represent subthreshold activity. The cooler the color, the lower the level of activity.

Spatio-temporal patterns of spiking or spiking-bursting activity in one dimensional signals are usually detected and analyzed by means of spectral methods. However, in higher dimensions, the coefficients produced by the multidimensional Fourier transform are hard to interpret. On the other hand, wavelet-based techniques have proven to be useful tools for signal analysis (Stollnitz et al., 1996; Mallat, 1999). Unlike the Fourier transform coefficients, the wavelet transform coefficients are determined both by a resolution component and a time (or space) component and, therefore, they represent the resolution content at a given portion of the original signal. Thus, to quantitatively characterize the bursting rhythmic activity in our network, we perform a wavelet-based analysis.

In particular, we use the same discrete wavelet transform (DWT) analysis employed in Latorre et al. (2013a) to characterize the global network dynamics of a model of the inferior olive. The method consists in considering the spiking-bursting spatio-temporal patterns produced by the network as sequences of images evolving in time. As a first step in the characterization, a two-dimensional basis is generated by direct Cartesian product of the one-dimensional Haar basis (Stollnitz et al., 1996). Then, the two-dimensional non-standard DWT is calculated for each frame of network activity. The idea behind this characterization method is that the number of wavelet coefficients in a given frame, C(t), provides an estimation of the complexity of the image corresponding to the spatio-temporal pattern at time t. A low number of coefficients means that the image is smooth or is composed of smooth components. In

contrast, a high number of coefficients corresponds to complex images. In this way, the DWT analysis transforms the multidimensional spiking-bursting activity in the network, $V_i(t)$, into a one-dimensional signal, C(t). This signal provides an useful characterization of the bursting dynamics in which both the frequency and the spatial complexity can be discussed. From the frequency perspective, a simple visual inspection of the evolution of C(t) allows to detect the presence of different rhythmic patterns in the network. Furthermore, these rhythms can now be studied by means of the one-dimensional Fourier transform. From the spatial complexity of the patterns, very high values of C(t) correspond to almost random behavior of every neuron, with no patterns present; intermediate high values indicate the presence of complex spatial structures in the patterns; while completely synchronized networks produce a small number of coefficients. Note, that C(t) ranges between 0 and the number of neurons in the network.

Spike-Timing Encoding Modality

The spike-timing encoding is related to the spreading of specific intraburst spike patterns through the network and the synchronization mechanisms that allow a group of neurons to recognize and emit the same signature at a given moment (Tristán et al., 2004; Carrillo-Medina and Latorre, 2015). To graphically illustrate the dynamic spatial organization of the spike patterns within the network, we generate activity movies representing the fingerprint-based evolving dynamics (e.g., see Figure 2.5). Each point in the 50×50 square represents with a color code the neural signature recognized by a given neuron within the network at a given moment. In this manner, neurons with the same color recognize the same signature. White color identifies the units that do not recognize any fingerprint.

To quantitatively analyze this encoding strategy, we compute the evolution of the number of neurons that recognize and emit each individual signature per time unit. This measure provides an estimation over time of the level of activity in the network related to each signature.

RESULTS

We have conducted experiments in which multiple datasets are presented to regular networks with different parameters. Independently of the network size and the number of neighbors per neuron, it is possible to find a broad range of synaptic weights and neuron parameters allowing the network to simultaneously encode information in the rhythmic and the spike-timing modality. However, the emerging phenomena that we describe here can be more easily illustrated in autonomous networks with a low level of bursting activity, since in these cases, the spatio-temporal activity in the different dimensions arises due to external stimulation. In autonomous networks, i.e., networks not receiving external input, the level of bursting activity depends on the transit probability of the internal state (p), the firing threshold (TH), and the duration of the refactory period (RP). These parameters modulate the ratio of bursts produced by an isolated neuron. The greater the value of the stochastic probability p, the higher the mean bursting frequency. Similarly, the bursting frequency also grows with low values of TH and RP.

Thus, in the following sections, we focus on neurons where $p = 0.05$, $TH = 50$, $RP = 50$, and $AP = 200$ (units are dimensionless). Note, that AP—the peak membrane potential to generate a spike—has no influence on information processing, the only requirement is being

greater than TH. We discuss results of square-shaped networks of 50 × 50 of such units, with periodic boundary conditions and where each unit is connected through an excitatory synapse (g_{ji} = 1) to its eight nearest neighbors as shown Figure 2.1C. External stimuli consist of tonic spiking signals at a given frequency introduced into a randomly chosen cell during a give time period. The neural signature of every neuron has six spikes, with all the ISIs in the range 2–12 (dimensionless). These signatures are randomly generated and assigned at the beginning of the simulation. The rest of parameters are specified in the corresponding experiment description. $V_i(0)$ is chosen randomly between 0 and 40 a.u. for all neurons in the network.

Rhythmic Encoding Modality

The degree of synchrony among the membrane potential of the neurons constituting the network characterizes the global spiking-bursting activity in the network. For fixed values of p and *TH*, the degree of synchrony varies as a function of the synaptic transmission strength among neurons (i.e., g_{ji} in Equation 3). For small values, each neuron fires nearly independently. As synaptic weights grow, the degree of synchrony increases because the generation of a burst in a given unit sequentially propagates to its neighbors and so on (Figure 2.2). The higher synchrony occurs in networks with combinations of firing thresholds and excitatory synapses that allow a target neuron to reach the firing threshold when it receives a burst ($g_{ji} \cdot \#spikes\_in\_burst \geq TH$). However, as we mention above, here we are interested in autonomous with a low level of bursting activity.

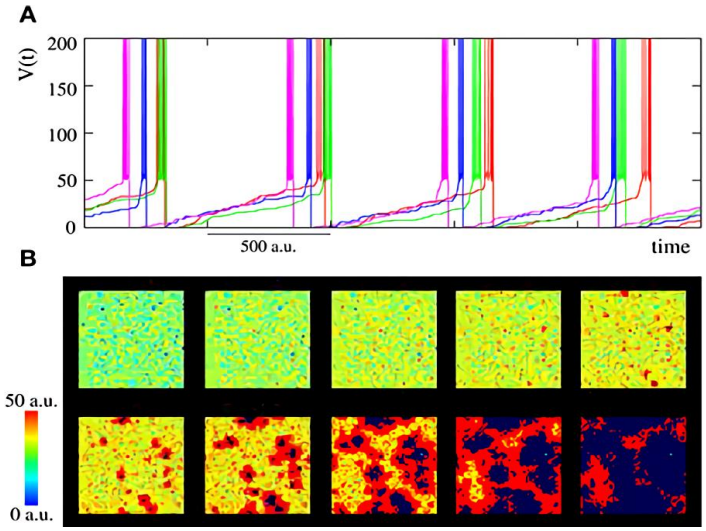

Figure 2.2 (A) Activity time series of four randomly chosen close neurons in an autonomous network with Mi = 400 and Li = 4. Units are dimensionless. Due to the synaptic excitation, the generation of a burst in a given unit propagates to the surrounding units. (B) Spatio-temporal patterns of spontaneous activity observed in the network of the top panel. The patterns consist of propagating wave fronts of spiking-bursting activity. Sequences develop in time from left to right and from top to bottom with a time interval between frames of 33 a.u.

Depending on the synaptic parameters, burst propagation provides autonomous networks the ability to generate well-defined spatio-temporal patterns in the form of propagating wave fronts of transient spiking-bursting activity. Note that local contextualization modulates intraburst firing patterns, but it has not any influence on burst timings. To illustrate these

spatio-temporal patterns, we generate activity movies representing the membrane potential evolving dynamics (see Section Rhythmic Encoding Modality for details). As representative example of the spontaneous collective bursting rhythms generated by the network, bottom panel in Figure 2.2 displays snapshots of the activity movie of the network shown in the top panel.

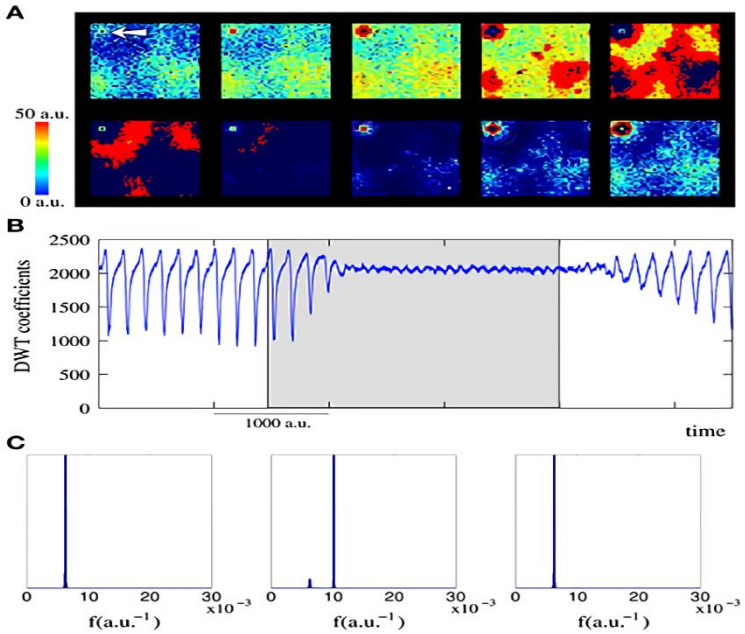

Figure 2.3 (A) Snapshots of an activity movie illustrating the spiking-bursting spatio-temporal patterns generated by the network of Figure 2.2 (M_i = 400 a.u. and L_i = 4) when a tonic input with a period of 100 time units between consecutive spikes is introduced into a single neuron (arrow in the first frame points to the neuron that receives incoming stimulus). Sequences develop in time from left to right and from top to bottom. The time interval between frames is 33 a.u. The stimulated unit increases its bursting frequency due to the external stimulation, and this generates new spatio-temporal patterns of transient spiking-bursting activity from this unit. (B) Characterization with the DWT coefficients of the activity of the network in the top panel: first without stimuli (snapshots in Figure 2.2B belong to this period), then when the selected neuron receives the incoming data (grayed area identifies the period while the input is active), and finally without any input again. (C) Normalized power spectra of the wavelet analysis for the three periods. Left: without stimuli. Middle: during the stimulation. Right: when the stimulation is over and after the reverberation period. Power spectra are calculated using time series of 500,000 time units. The DWT analysis demonstrates that the global network dynamics changes when data are introduced into the network. It also shows that the network is a dynamical working memory of spiking-bursting rhythms, since the network dynamics generated in response to data onset reverberates after the input is retired.

The spontaneous generation of transient spatio-temporal patterns of spiking or spiking-bursting activity is a feature with relevant functional implications observed in different living neural media. However, we are interested in the network response to stimuli. Therefore, from the encoding perspective, the most interesting feature of the network, appearing even in networks with a small synaptic transmission among neurons, is its ability to develop dynamical patterns of spiking-bursting activity in response to data onset. These patterns allow the network to encode information using the frequency of different bursting rhythms induced by stimuli. To illustrate how the network of Figure 2.2 encodes a single input using this spatio-temporal space, Figure 2.3A shows snapshots of its collective spiking-bursting dynamics when a unit in the left-top corner receives an external tonic spiking signal. When the stimulus is

introduced into the neuron, its firing frequency increases. Then, the spiking-bursting activity originated in the stimulated neuron propagates to the surrounding units because of excitation. Thus, this neuron becomes the origin of a new rhythm that coexists with those generated spontaneously by the network (if any).

The DWT analysis (Section Rhythmic Encoding Modality) corroborates the rhythm encoding in the network transient spiking-bursting dynamics. Changes in the collective spiking-bursting dynamics in response to data onset are reflected in a change in the evolution of the DWT coefficients whose shape characterizes the spiking-bursting activity of the network. As an example, Figure 2.3B illustrates how the collective dynamics of the network in Figure 2.3A changes when data are introduced into the stimulated unit. Initially, no data is present and the network spontaneously generates spatio-temporal patterns as the ones shown in the bottom panel of Figure 2.2. In this situation, the DWT coefficients oscillate with a nearly homogeneous frequency capturing the spontaneous spiking-bursting rhythm. The spontaneous rhythm frequency depends on the stochastic probability p and can be estimated by means of the Fourier transform of the wavelet analysis of the network activity. For instance, in the network of Figures 2.2, 2.3, the spontaneous rhythm frequency is around $6.2 \cdot 10^{-3}$ (see frequency peak in Figure 2.3 C, left). On the other hand, the oscillation of the DWT coefficients between a high and an intermediate value indicates, respectively, the nearly independent neuron behavior during subthreshold activity and a high transient synchronization in the network during the spreading of the spiking-bursting wave fronts. Then, the external stimulus is introduced into the network during a given time interval (grayed area). At this point, the network collective dynamics stepwise changes. A first remarkable change in the evolution of DWT coefficients is observed in the oscillation amplitude. Now, the DWT coefficients tend to oscillate around two high values. This change points out the complex spatial structure of the new emerging dynamics. Not obtaining low or intermediate values in the DWT analysis during the stimulation period indicates that, in this network, the propagation of the wave fronts originated in the stimulated unit does not imply a complete transient synchronization in the whole ensemble. Another relevant change in the DWT coefficients during the stimulation is a frequency increase (cf. left and middle power spectra in Figure 2.3C), pointing out that the rhythm evoked by the stimulus prevails over the spontaneous rhythm ($6.2 \cdot 10^{-3}$ vs. $10 \cdot 10^{-3}$ a.u.$^{-1}$). The frequency of the spiking-bursting rhythms evoked by external stimulation depends on the frequency of the input, since the stimulated neuron follows the stimulus. These changes indicate that the network has encoded the incoming information in a characteristic spiking-bursting rhythm. Finally, no input is present again and the network recovers the spiking-bursting autonomous activity (cf. Figure 2.3C, right). The DWT analysis indicates that the stimuli-evoked rhythms can reverberate for long periods after data onset. This implies that the network behaves as a working memory in the spiking-bursting spatio-temporal space. For each network configuration, the mean reverberation period of the rhythms encoding different inputs is nearly the same, i.e., the memory capability of the network in this information dimension is independent of the data and only depends on the synaptic parameters.

The emerging collective dynamics analysis in networks that receive multiple tonic stimuli with different frequencies indicate that spatio-temporal patterns of spiking-bursting activity allow the network to encode information using several coexisting and coordinated rhythms. Top panel in Figure 2.4 displays an example of the complex spatial organization of the patterns generated by a network receiving 10 different inputs. The snapshots clearly show the increased

complexity of the patterns, since, now, the network organizes clusters of neurons oscillating at different frequencies (cf. top panel in Figure 2.3). Each of the unit receiving external data becomes the source of a rhythm that propagates through the network competing with the rhythms encoding other inputs. As we show above, while an input is active, the corresponding rhythm survives in the network. Therefore, when more than one stimulus is present, the competition among the input-evoked spiking-bursting rhythms is a winnerless competition. Note that there is no inhibition in the network nor subcellular plasticity rules limiting the spiking-bursting activity. Winnerless competition allows the encoding of multiple coexisting spiking-bursting rhythms. This competition dynamics is captured by the DWT analysis (bottom panel in Figure 2.4). When multiple data are introduced into the network, the number of DWT coefficients remains high with a non-homogeneous oscillation frequency. This reveals the complex spatial structure of the patterns and, on the other hand, the coexistence of multiple spiking-bursting rhythms within the network.

We have previously shown that the spiking-bursting rhythms evoked by a single stimulus reverberate for a while when the stimulation is over. The reverberation period drastically increases when the network receives multiple stimuli. The greater the number of external inputs, the greater the number of sources of spiking-bursting activity. This translates into a higher spiking-bursting activity in the network and explains the increasing reverberation period. Depending on the synaptic strength and the value of p, in this situation, the network even becomes a long-term memory of spiking-bursting rhythms. We would like to emphasize that the rhythms that survive for longer periods in short-term memories or the ones that persistently reverberate in long-term memories are not always the higher frequency stimuli-evoked rhythms nor the rhythms encoding the last data presented to the network.

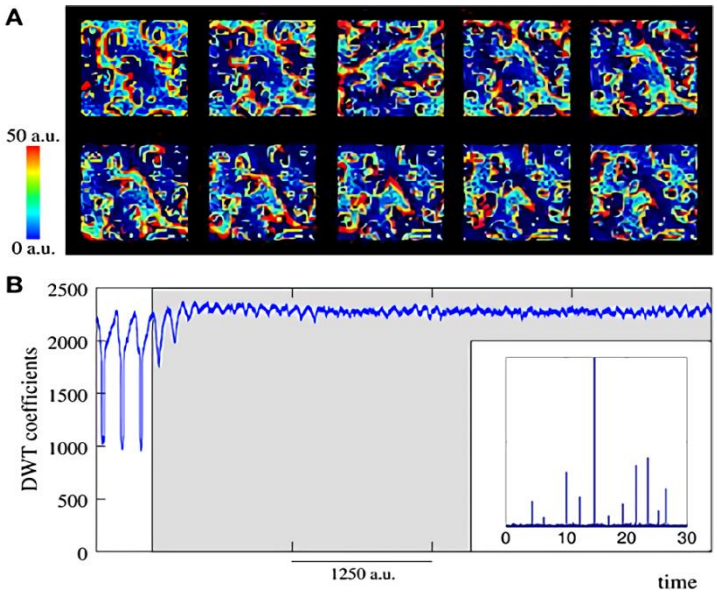

Figure 2.4 Figure equivalent to Figure 2.3 but when the network (M_i = 400 a.u. and L_i = 4) receives 10 inputs. (A) Sequences develop in time from left to right and from top to bottom. The time interval between frames is 33 a.u. In response to data onset, the network starts generating 10 different coexisting rhythms encoding incoming information. (B) The different spiking-bursting rhythms encoded within the network are captured by the DWT analysis. While external inputs are present, the oscillation frequency of the DWT coefficients is not homogeneous (see inset), which reveals the coexistence of the different rhythms. Inset shows the normalized power spectrum of the wavelet analysis of a time series of 500,000 time units while the 10 external stimuli are present. The number of coefficients increase (cf. Figure 2.3B) denotes the increase in the spatial complexity of the patterns.

Spike-Timing Encoding Modality

One of the major characteristics of the proposed network is the intra-unit contextualization of input signals, responsible of the spike-timing encoding modality. In this section, we study the complex collective dynamics induced by this intra-unit information processing strategy. These emerging collective dynamics can give us important clues about the underlying computational properties of the network.

As expected, the ability of an individual unit to recognize specific fingerprints varies as a function of the intra-unit parameters shaping local contextualization, i.e., the maximum size of the local informational context (M_i) and the fingerprint learning threshold (L_i). Depending on the value of these parameters, specific intraburst firing patterns can propagate through autonomous networks. However, the more interesting phenomena from the information processing viewpoint are related to the mechanisms that allow the network to generate and organize spatio-temporal patterns in response to data onset. Therefore, we focus our attention on networks in which the signature recognition does not occur without external stimuli. When these networks receive incoming data, they aid the study of the information encoding in the fingerprint-based spatio-temporal space by analyzing how the signatures of the stimulated units propagate throughout the network.

Again, we first address the analysis of networks receiving a single stimulus. When a neuron receives an external tonic input, this unit increases its bursting frequency (see Section Results: Rhythmic Encoding Modality). This increase can make the neighbor units recognize the neural signature of the stimulated neuron and propagate the corresponding intraburst firing pattern. In this situation, new intriguing collective dynamics arise in the network. To illustrate the dynamic spatial organization of the neural signatures traveling through the network, we generate activity movies representing the fingerprint-based evolving dynamics (see Section Spike-Timing Encoding Modality for details). These activity movies point out that the network generates in this dimension well-defined transient patterns of activity in response to data onset. The emerging spatio-temporal patterns are related to the spatial organization and clusterization of the signatures traveling through the network. To give insight into the generation and propagation of these complex spatio-temporal structures, Figure 2.5 shows snapshots of the activity movies of two representative networks in which the same unit receives an input. Note, that the only signature traveling through the network corresponds to the stimulated unit. If we consider that at a given moment two neurons that recognize the same signature belong to the same cluster; we can study the specific properties of the dynamic organization of the patterns by calculating the clustering coefficient and the average shortest path between neurons belonging to the same cluster. This analysis indicates that the fingerprint-based spatio-temporal patterns are initially originated in the stimulated unit (see initial frames in the sequences of Figure 2.5). Then, depending on the parameters M_i and L_i, they can propagate locally or globally as transient wave fronts; or as localized clusters with a fixed spatial organization that occasionally become the source of new transient patterns. The generation of localized transient patterns of activity in the fingerprint spatio-temporal space suggests a collective coding strategy based on the emission and recognition of specific neural fingerprints. This mechanism allows the network to encode information regarding the origin of incoming data (input source) in a distributed network form.

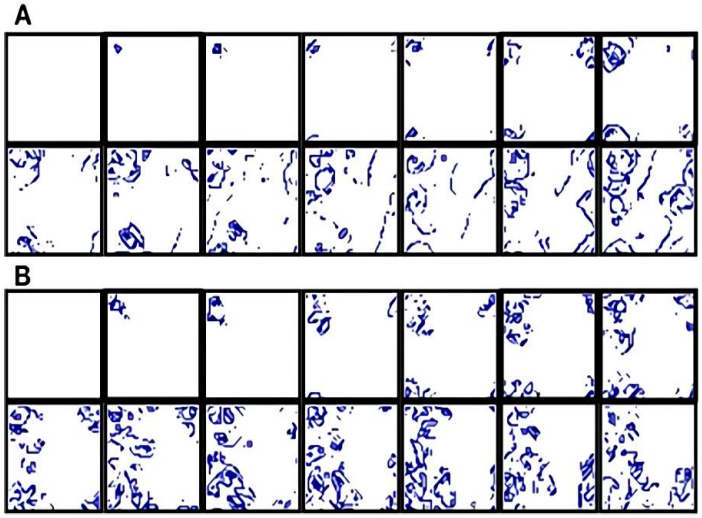

Figure 2.5. Snapshots of two representative activity movies illustrating the fingerprint-based encoding mechanism. (A) M_i = 500 a.u. and L_i = 5. (B) M_i = 400 a.u. and L_i = 4. Sequences develop in time from left to right and from top to bottom. The time interval between frames is 1000 a.u. Note that the propagation of the fingerprint-based spatio-temporal patterns is slower than the corresponding spiking-bursting rhythms (cf. bottom panel and Figure 2.3). The color code identifies neurons recognizing the same signature, being white color used for neurons that do not recognize any signature. The first frame in each sequence indicates that, in the absence of stimuli, neural signatures do not propagate in these networks. When the external stimulus is introduced into a neuron located in the left-top corner (second frame in both panels), new collective dynamics emerge and the network organizes transient spatio-temporal patterns of activity related to the propagation of the signature of the stimulated unit (blue regions). Note that this is the only signature that travels throughout the network. These localized patterns of activity encode the who of incoming data.

The information encoded in the spike-timing modality and the encoded in the rhythmic modality coexist in the network. A relevant property observed in the simulations is that a neural fingerprint does not necessarily travel over the propagating wave fronts encoding the corresponding spiking-bursting rhythm. The spreading velocity of the fingerprint-based spatio-temporal patterns is always slower than the corresponding spiking-bursting spatio-temporal patterns velocity (cf. time interval between frames in Figures 2.3, 2.5; 33 vs. 1000 a.u). Likewise, the spatial organization of the patterns in the different spatio-temporal spaces is not correlated. If we consider that at a given moment two neurons over the firing threshold belong to the same cluster, we can calculate the clustering coefficient and the average shortest path for the spiking-bursting patterns and compare the self-organizing properties of the patterns encoded in both information dimension. This analysis points out that the spiking-bursting patterns always consist of propagating transient wave fronts from the stimulated unit traveling through the whole network. Meanwhile, the fingerprint-based patterns can also be originated in the stimulated unit, but they can propagate locally or globally as transient wave fronts or remain bounded in specific regions of the network.

A simple way to characterize the fingerprint-based dynamics is computing the number of neurons that recognize and emit a given firing pattern. This allows us to identify the signatures encoded in the network. Figure 2.6A depicts the characteristic evolution of the level of activity related to the fingerprint of the data source in three representative networks receiving the same single input during three different stimulation periods. This figure corroborates the results derived from the snapshots shown in Figure 2.5. When the stimulation begins, the signature of the stimulated unit starts propagating through the network. The number of

neurons recognizing this fingerprint grows until reaching a stationary level that depends on the value of M_i and L_i. Then, the network dynamics consists of a fluctuation around the steady level (e.g., see blue traces in Figure 2.6A). This dynamic is kept while the stimulation is sustained. When the stimulation ends, the stimulus-evoked activity does not immediately disappear from the network (cf. red and green traces in Figure 2.6A). This is an interesting result that demonstrates that intra-unit contextualization can be a mechanism to implement intrinsic memory in the network, giving rise to both short-term and long-term memories. In short-term memories (bottom and middle panel in Figure 2.6A), the stimuli-evoked dynamics reverberate for a while. This reverberation effect constitutes a mechanism providing the network the ability of acting as a dynamical working memory that transiently stores incoming data. In contrast, in long-term memory networks (top panel in Figure 2.6A), the information survives in the network in a permanent manner (maybe until a new input is received).

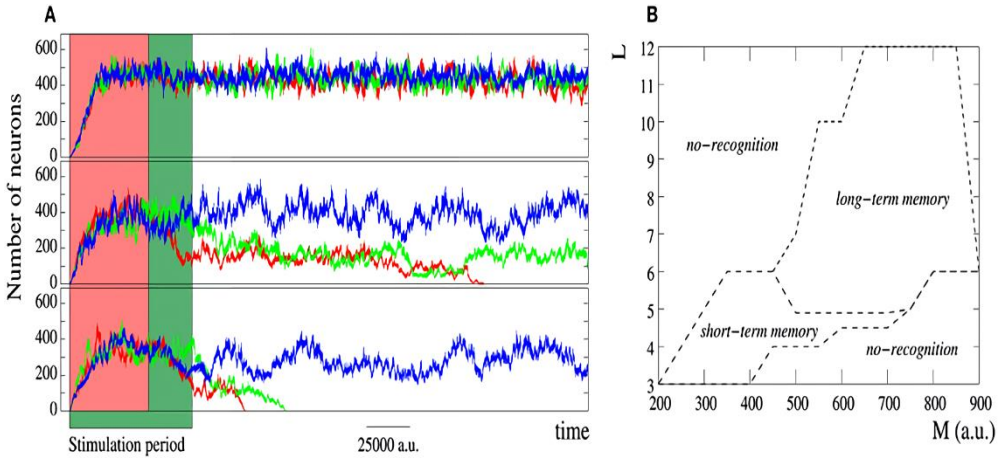

Figure 2.6. (A) Evolution of the mean number of neurons that recognize and emit the fingerprint of a unit receiving the same data in three different networks during three different periods. Each trace is calculated as the average of 10 experiments with different random seeds and location of the stimulated unit. These plots characterize the stimuli-evoked fingerprint-based dynamics. Top panel: M_i = 500 and L_i = 5. Middle panel: M_i = 400 and L_i = 4. Bottom panel: M_i = 350 and L_i = 4. Units are dimensionless. In red traces, the stimulation period corresponds to the red region. In green traces, to the green region. And in blue traces, data are continuously present. In this spatio-temporal space, the network may act as a long-term memory (top panel) or as a short-term memory (middle and bottom panels) depending on the value of M_i and L_i, i.e., the parameters associated to intra-unit contextualization. (B) Phase diagram illustrating the relationship between M_i and L_i in networks where p = 0.05, TH = 50, RP = 50, and AP = 200 (units are dimensionless).

The collective dynamics in the fingerprint-based dimension is mainly driven by the intra-unit parameters M_i and L_i. On the one hand, reducing the size of the local informational context of every neuron (M_i) decreases the number of neurons that recognize a given firing pattern. On the other hand, decreasing the learning threshold (L_i) facilitates the recognition of the propagating fingerprints and, therefore, the level of activity in the network grows. The trade-off among the effect of these parameters determines if the network encodes information in the spike-timing modality and the mode of behavior in this dimension. To illustrate this, Figure 2.6B depicts a phase diagram locating the different behaviors in the space of intra-unit parameters.

With the experiments described so far, we investigate the ability of the proposed network to encode and process a single stimulus using an information processing strategy driven by local contextualization. If we repeat the same experiments but now introducing multiple

inputs simultaneously, we observe that the presence of multiple stimuli makes the network generate coexisting transient spatio-temporal patterns of activity encoding the origin of the different inputs (Figure 2.7). These experiments reveal additional relevant computational properties that subcellular plasticity can provide to spiking neural networks. When multiple intraburst firing patterns spread through the network, a competition dynamic arises between them. A simple visual inspection of the snapshots shown in Figure 2.7 reveals that the self-organizing properties of the patterns drastically change depending on the intra-unit parameters shaping the intra-unit plasticity rules. These define different modes of competition among the spreading fingerprints. This competition affects the global level of activity of each signature in the network and determines the spatial organization of the patterns. The competition dynamics among the different intraburst firing patterns determines the coherence and coordination of the coexisting patterns.

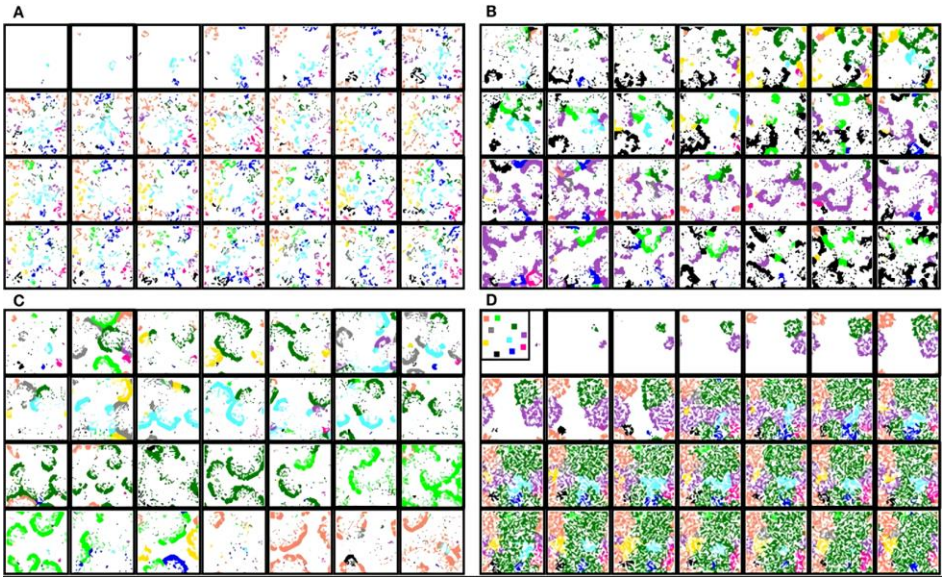

Figure 2.7 Snapshots of four representative activity movies illustrating the fingerprint-based spatio-temporal patterns generated by networks that receive 10 data simultaneously. The inset in the first frame of (D) shows the approximate location of each input. Sequences develop in time from left to right and from top to bottom. The time interval between frames is 2000 a.u. Subcellular plasticity induces different competition dynamics among the coexisting patterns in this spatio-temporal space: from winnerless (A–C) to winner-take-all (D). These competition regimes are characterized in Figure 2.8. (A) $p = 0.05$, $M_i = 400$, and $L_i = 4$. The competition among fingerprints makes the patterns only propagate locally, remaining bounded near the corresponding stimulated unit. (B) $p = 0.05$, $M_i = 350$, and $L_i = 4$. Evolving coexisting patterns propagate through the whole ensemble. Each pattern is originated in the unit that receives the corresponding input. (C) $p = 0.05$, $M_i = 500$, and $L_i = 5$. The patterns also travel through the whole network, but there exist alternating periods during which only the patterns encoding a given input propagate. After that, a new competing cycle begins until a fingerprint prevails over the others and starts propagating. (D) $p = 0.08$, $M_i = 350$, and $L_i = 3$. As result of the competition, only the patterns associated to a limited group of data (the winners) propagate. Note that the different competition regimes arise depending on the values M_i and L_i which shape the intra-unit contextualization mechanism.

We would like to highlight that the competition regimes observed in the activity movies arise in the absence of inhibitory connections, which hints at intra-unit contextualization as an effective mechanism to restrict the activity in networks without inhibition. Note that each neuron can only transmit one recognized firing pattern per burst. This limitation produces somehow a local competition among the patterns received by the neuron where only the "winner" is transmitted. This local competition is the basis of the global competition in the

whole network.

The different dynamical modes observed in the activity movies are better characterized by the evolution of the number of neurons that recognize and emit each signature (Figure 2.8). Regardless the number of active inputs, the type of competition depends on the value of the parameters M_i and L_i and may vary from a winnerless (WLC) to a winner-take-all (WTA) competition. In WLC networks, none of the signatures becomes a "winner," and therefore, none of them persistently prevails over the others. Depending on the intra-unit parameters, the network can display different winnerless regimes. Figure 2.8A illustrates a winnerless competition in which the level of activity related to every fingerprint is similar and remains fluctuating nearly a stationary level. This defines a collective dynamic where several coherent spatio-temporal patterns coexist within the network encoding simultaneously a great amount of data (e.g., in Figure 2.8A all the inputs introduced into the network). Figures 2.8B, C show winnerless regimes with alternating periods where some fingerprint has a higher level of activity.

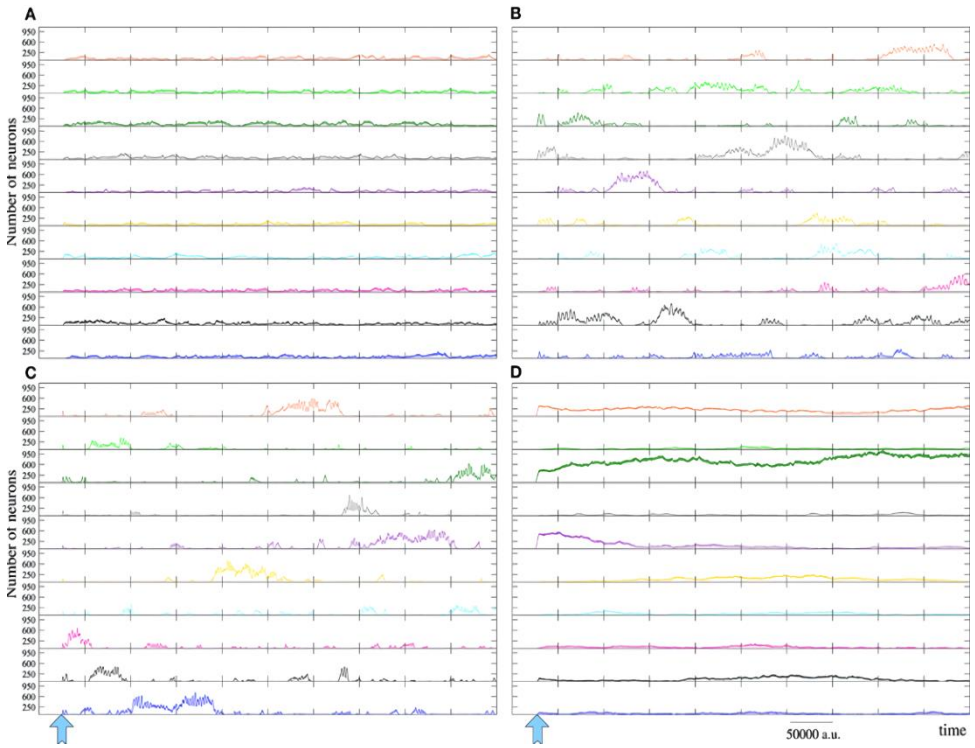

Figure 2.8 Level of activity related to the 10 neural signatures belonging to the input sources in the networks of Figure 2.7. The inputs and the color code used to identify them are the same used in this figure. All of them are injected simultaneously from time step pointed out by the arrow to the end of the time series. Each panel corresponds to the equivalent in Figure 2.7 and illustrates a different competition regime (see main text for details).

An interesting phenomenon observed with some network settings is that some regions within the network specialize in the emission of firing patterns encoding the origin of different stimuli although they do not receive any external input. This phenomenon occurs without any kind of supervised synaptic nor intra-cellular learning, i.e., it is a self-organizing property of the network. These emitter areas are usually related to winnerless competitions where the prevailing fingerprints change accordingly to the patterns originated in these areas

(Figure 2.9). Conversely, when a winner-take-all competition occurs, only the signature or signatures that win the competition propagates through the network (e.g., see Figure 2.8D). In the WTA network shown in Figure 2.7D, all the neurons tend to recognize and emit simultaneously the prevailing fingerprint. However, depending on M_i and L_i, this can also spread as evolving transient patterns equivalent to the shown in Figure 2.7C when the dark green input prevails over the others. Note that, in some sense, the winnerless competitions displayed in Figures 2.7B, C consist of sequences of transient winner-take-all competitions.

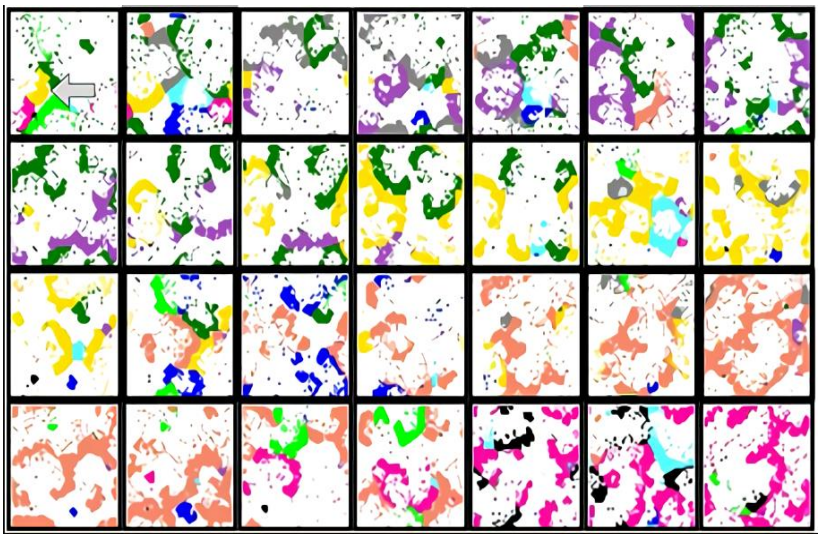

Figure 2.9 WLC network whose collective dynamics is characterized by an emitter area that generates transient patterns encoding the prevailing fingerprint in the network. Arrow in the first frame denotes the approximate location of this area. Sequences develop in time from left to right and from top to bottom. When neurons in the pointed area start generating patterns encoding a given input, the collective behavior changes accordingly to these patterns and the corresponding fingerprint prevails over the others. Note that the existence of these emitter areas is a self-organizing property of the network.

The reverberating spatio-temporal patterns encoding the origin of incoming data continue competing even when they are not sustained by an active input. Short-term memory networks have a limited ability to retain previously stored data when new information is introduced into the network. In these cases, the reverberation period drops as compared to networks receiving a single input, and the stored data are almost instantaneously forgotten, i.e., the corresponding patterns disappear because the patterns encoding the last incoming stimulus win the competition. However, in long-term memory networks, coexisting coherent spatio-temporal patterns related to multiple fingerprints can be observed even when the corresponding input is not active.

DISCUSSION

The present work introduces a spiking neural network that makes use of multicoding strategies for information propagation and subcellular plasticity to locally contextualize or discriminate data received by a unit. Furthermore, each neuron in the network has a neural signature that allows its unequivocal identification by the rest of the cells. This network is an encoder and generator of spatio-temporal patterns that take advantage of the multiple simultaneous encoding modalities present in the network to transform dynamic inputs into different spatio-

temporal spaces, and organize and coordinate coexisting patterns of transient activity in response to data onset.

The discussed experiments are aimed at analyzing the emerging collective dynamics in two information dimensions. On one hand, a spiking-bursting spatio-temporal space, where information processing is driven by synaptic transmission. On the other hand, a fingerprint-based spatio-temporal space driven by an intra-unit contextualization mechanism. The specific properties of the dynamic organization of the patterns are different in each information dimension, so that, the life cycle of the information encoded in both encoding schemes is independent. When multiple patterns in the same dimension coexist in the network, a competition emerges between them. We show that various forms of competition can arise without inhibitory connections in the network. Depending on the parameters shaping simple intra-unit plasticity rules, the competition regime may vary from a winnerless (i.e., the network stores multiple data simultaneously) to a winner-take-all competition (i.e., one datum or a group of them prevails over the others). The stimuli-evoked spatio-temporal patterns and the corresponding competing dynamics can survive for long periods after data onset. This reverberation effect allows the network to memorize incoming data. This can display short-term or long-term memory capabilities in the different spatio-temporal spaces. When the network behaves as a short-term memory, the spatio-temporal patterns encoding incoming data in the corresponding scheme transiently reverberate after the stimulation ending. Conversely, in long-term memories, the stimulus leads the network to a new stable state and the patterns persistently survive. The memory ability of the network in each dimension varies as a function of the synaptic and/or intra-unit parameters. Therefore, different simultaneous processing strategies can be implemented within the network.

These results illustrate the dynamical richness and large flexibility of the proposed network to encode and process information in different spatio-temporal spaces. We argue that plasticity mechanisms inside individual cells and multicoding strategies can provide additional computational properties to spiking neural networks, which could enhance their capacity and performance. In particular, local contextualization mechanisms allow individual neurons to process the multiple simultaneous codes in their input signals selectively or globally in order to completely decide or weight the decision about their output in the different encoding schemes. This information processing provides a framework to model complex high-dimensional processes that can be applied to different real-world computational problems. The ideas relating multicoding with local information discrimination have a direct application in problems that benefit from multifunctionality and parallelism. These are desirable features for many technical applications of ANNs, representing a potential advantage when processing large amounts of data or multiple decision-making criteria must be developed, for instance, in multiobjective optimization problems (Saini and Saraswat, 2013; Wang *et al.*, 2014) or in control systems [e.g., multifunctional prosthesis controllers that must quickly detect and classify multiple characteristic simultaneous myoelectric signals (Saridis and Gootee, 1982; Hudgins *et al.*, 1993; Karlik *et al.*, 2003; Li *et al.*, 2010)]. Another straightforward application of these concepts is in problems where a global task is solved by means of solving independent partial tasks. An example is the wide scope of multidimensional sorting problems, specifically when the order in a particular dimension can be independent of the order in other dimensions, or when there are no global sorting criteria in any dimension. Non-spiking signatures neural networks have been successfully applied to this type of problems (Latorre *et al.*, 2011). Areas of application for multidimensional sorting are scheduling, planning and optimization,

between others (Catoni, 1998; Aref and Kamel, 2000). On the other hand, the different dynamical modes observed in the network are relevant in the context of multiple technical applications. Winnerless competition is usually associated to sequential information processing (Seliger *et al.*, 2003; Rabinovich *et al.*, 2006a; Arena *et al.*, 2009; Kiebel *et al.*, 2009; Latorre *et al.*, 2013b), which has a wide application in many artificial intelligent systems in tasks such as inference, planning, reasoning, natural language processing, and others (Sun and Giles, 2001; Wörgötter and Porr, 2005). Similarly, pattern recognition in different spiking ANNs is based on winner-take-all dynamics (Bohte *et al.*, 2002a; Gütig and Sompolinsky, 2006; Schmuker *et al.*, 2014).

In this paper, we have imposed some constraints and assumptions in order to facilitate the presentation of our results. Results obtained with larger regular networks (up to 1000×1000); higher levels of bursting activity; and different number and/or distribution of spikes in the neural signatures are equivalent to the results presented in Section Results. In experiments with signatures with an arbitrary number of spikes, new interesting fingerprint-based dynamics emerges in the network and results are not exactly the same. In these simulations, not only the fingerprints belonging to a neuron propagate, but also specific firing sequences built with combinations of these signatures propagate throughout the network. In some sense, these networks do not only encode information regarding the input source, but they also generate new information. It is also important to note that, for simplicity, we only consider two encoding schemes in the network. However, bursting activity allows easily including additional units of information (e.g., the burst duration or the number of spikes in the burst). In this line, and regarding a selective processing of input messages, experimental evidence indicates that some neural systems exhibit functional or behavioral neural signatures representing different states or associated to the task performed at a given moment (Klausberger *et al.*, 2003; Somogyi and Klausberger, 2005; Kaping *et al.*, 2011). The concept of neural fingerprint that underlies the strategy of the discussed network can be extended to consider the emission and recognition of multiple fingerprints with a different meaning within the same signal. In this situation, subcellular plasticity in the form of intra-unit information contextualization mechanisms would allow individual neurons to perform a distinct processing of incoming signals, for example, as a function of specific emitters and/or functional states.

Although not addressed in this paper, subcellular plasticity and multicoding mechanisms for information processing can be combined with the features that underlie information processing in the existing spiking neural network paradigms. In this line, for example, plenty of work has been done on synaptic plasticity in spiking neural networks, since modifications of the synaptic connections are traditionally considered the physiological basis of learning in the nervous system. These works are mostly related to unsupervised synaptic learning methods, such as Spike-Timing Dependent Plasticity (STDP) (Song *et al.*, 2000; Bohte *et al.*, 2002b; Kube *et al.*, 2008; Meftah et al., 2010), with an increasing interest into supervised synaptic learning (Bohte *et al.*, 2002a; Belatreche *et al.*, 2007; Yu *et al.*, 2013). The combination of learning rules including not only the modification of the synaptic weights, but also the parameters that affect the local discrimination of input signals can greatly contribute to enhance the spiking ANNs' computational power. In this vein, our results can be of particular interest in the context of the generation and recognition of spatio-temporal information. Different spiking neural networks have been proposed to process, classify, and store spatio-temporal patterns (Laje and Buonomano, 2013; Yu *et al.*, 2013). We speculate that incorporating multicoding strategies and different types of subcellular plasticity to other

successful spiking ANN paradigms can potentially allow these networks to process, classify and store more complex data. For example, a highly relevant application of the referred spiking networks is the analysis of EEG spatio-temporal data. To consider a multicoding mechanism that incorporates the neural fingerprint-based dimension to these networks could permit an analysis of coexisting brain rhythms from multiple simultaneous perspectives. In particular, the fingerprint-based spatio-temporal patterns could facilitate the analysis of the propagation trajectories and the identification of possible information sources and sinks in different cognitive processes.

Because of their functional similarity to biological neurons, spiking neural networks have been extensively used by the computational neuroscience community as a powerful tool for studying neural information processing (e.g., see Izhikevich, 2003; Deco *et al.*, 2008; Izhikevich and Edelman, 2008). Results obtained with our simple model could also be relevant from this perspective Information storage in the nervous system has been typically studied considering the adaptation of the synaptic connection strengths (e.g., see Zipser *et al.*, 1993). Our simulations suggest that mechanisms inside individual cells modulating their intrinsic dynamics could also be an effective mechanism to implement intrinsic memory, both in short- and long-term memory networks. On the other hand, many biological neural systems (including many areas of the human brain) continuously receive a great amount of inputs from many different sources and, nevertheless, they exhibit a low level of activity and only respond to specific inputs (Shoham *et al.*, 2006; Sato *et al.*, 2007; O'Connor *et al.*, 2010; Barth and Poulet, 2012). We hypothesize that neural dynamics based on the propagation of specific neural fingerprints and a contextualization mechanisms like the one studied here could explain why these system are so sparsely active. Target neurons would only fire when they recognize a characteristic firing pattern in their incoming stimuli; while signal not recognized would be simply ignored. Obviously, to test this hypothesis more realistic spiking models for the activity of the neurons must be developed.

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Capítulo 3

Detección de secuencias de activación en neuronas spiking-bursting por medio del reconocimiento de firmas neuronales intraburst

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RESUMEN

La actividad *bursting* o en ráfagas está presente en multitud de células de diferentes sistemas neuronales y juega un papel muy importante en el procesamiento de información. Existen muchos ejemplos de agrupaciones de neuronas bursting que actúan de forma cooperativa para producir patrones espacio-temporales coordinados de actividad secuencial. Uno de los principales objetivos de la Neurociencia es la comprensión de los mecanismos subyacentes al procesamiento de información neuronal basado en este tipo de dinámica secuencial. Descubrimientos experimentales han revelado la presencia de patrones de disparo dentro de las ráfagas de algunas células bursting característicos de determinados tipos/familias de células. Estas firmas neuronales características coexisten con la información codificada en otros aspectos de las señales spiking-bursting. Desde el punto de vista biológico, todavía no está claro si las firmas neuronales tienen algún significado funcional. Desde esta perspectiva funcional, en este trabajo simulamos e investigamos la capacidad de un modelo de neurona basado en conductancias de detectar secuencias de activación presináptica específicas aprovechándose de la presencia de firmas intraburst que identifiquen el origen de las señales que conforman un patrón de actividad secuencial. Nuestras simulaciones muestran que una neurona lectora podría utilizar la información codificada en determinaos patrones de disparo intraburst para contextualizar las señales entrantes y, en consecuencia, calcular una respuesta característica basándose en relaciones de fase precisas entre la actividad rítmica de diferentes neuronas. Este tipo de mecanismos proporcionaría a las neuronas individuales una mayor capacidad para controlar y negociar la generación de dinámica secuenciales complejas. En este sentido, discutimos las posibles implicaciones de este mecanismo de contextualización para el procesamiento de información neuronal

DETECTION OF ACTIVATION SEQUENCES IN SPIKING-BURSTING NEURONS BY MEANS OF THE RECOGNITION OF INTRABURST NEURAL SIGNATURES

Abstract Bursting activity is present in many cells of different nervous systems playing important roles in neural information processing. Multiple assemblies of bursting neurons act cooperatively to produce coordinated spatio-temporal patterns of sequential activity. A major goal in neuroscience is unveiling the mechanisms underlying neural information processing based on this sequential dynamic. Experimental findings have revealed the presence of precise cell-type-specific intraburst firing patterns in the activity of some bursting neurons. This characteristic neural signature coexists with the information encoded in other aspects of the spiking-bursting signals, and its functional meaning is still unknown. We investigate the ability of a neuron conductance-based model to detect specific presynaptic activation sequences taking advantage of intraburst fingerprints identifying the source of the signals building up a sequential pattern of activity. Our simulations point out that a reader neuron could use this information to contextualize incoming signals and accordingly compute a characteristic response by relying on precise phase relationships among the activity of different emitters. This would provide individual neurons enhanced capabilities to control and negotiate sequential dynamics. In this regard, we discuss the possible implications of the proposed contextualization mechanism for neural information processing.

Keywords Sequential activity · Neural signatures · Preferred input-output relation · detection of activation sequences · Local contextualization · Sequential dynamics

From a functional point of view, action potentials or spikes are informational events that allow individual neurons to compute and communicate by transforming synaptic input into output spike patterns. A common feature of the temporal organization in the firing pattern of many neurons consists of grouping individual spikes into bursts separated by quiescent periods in the so-called spiking-bursting activity (Izhikevich, 2006). The role of burst firing has been discussed in the context of many different neural systems. Bursts of spikes have been traditionally considered as unitary events that are treated as a whole by the reader of the neural signal. From this perspective, the importance of the slow depolarizing wave in neural bursting behavior and the role it plays in the communication between bursting cells is well-known [e.g., see refs (Lisman, 1997; Reinagel *et al.*, 1999; McCormick and Contreras. 2001; Sherman, 2001; Eyherabide *et al.*, 2008; Sabourin and Pollack, 2009)]. Nevertheless, spiking-bursting activity involves the presence of at least two different time scales that can serve to encode distinct informational aspects: one related to the slow depolarizing bursting period and another related to the fast intraburst spiking timescale. Only in recent years the role of fast dynamics in bursting neurons is receiving some attention. For instance, experimental and modeling studies have addressed the encoding of different stimuli by means of specific intraburst spike patterns (IBSPs) (Kepecs and Lisman, 2003; Khosravi-Hashemi and Chacron, 2012); the effect on the muscle response of certain intraburst properties such as the interspike frequency or the number of spikes per burst (Morris and Hooper, 1997; Morris *et al.*, 2000; Zhurov and Brezina, 2006; Brezina, 2007), the existence of channel-specific information discrimination mechanisms at the single-cell level depending on the timings within a spike train (Chabrol et al., 2015; Latorre et al., 2016); or the selective response of a postsynaptic neuron to specific interspike frequencies (Izhikevich *et al.*, 2003; Krahe and Gabbiani, 2004). Of particular interest in this context is the observation of robust cell-specific intraburst firing

patterns in both invertebrates and vertebrates neurons (Szücs *et al.*, 2003; Szücs *et al.*, 2005; Garcia *et al.*, 2005; Zeck and Masland, 2007). These characteristic IBSPs can be considered a neural signature that allows us to identify the signal source. Some intraburst signatures are robust and reproducible even across different species (Brochini *et al.*, 2011). The observation of these fingerprints in widely different neural systems and their conservation in evolution raise several intriguing questions related to the existence of mechanisms to identify the origin of a neural signal and to the information processing based on this identification. Furthermore, the generation of a neural signature in living cells coexists with the encoding of information in other informational aspects of the bursting signal, e.g., the slow depolarizing wave. This hints at the use of a multiplexed encoding strategy where the neuron identity could be transmitted together with a content message (Latorre *et al.*, 2006; Latorre *et al.*, 2007b). The use of multiplexed codes in the same signal has been discussed in different sen sory and motor networks (Friedrich *et al.*, 2004; Kayser *et al.*, 2009; Panzeri *et al.*, 2010; Gire *et al.*, 2013; Clemens *et al.*, 2015; Hong *et al.*, 2016). Multicoding strategies for information propagation can greatly enhance the computational capacity of neural systems, as they allow transmitting and processing multiple information simultaneously (Blumhagen et al., 2011; Ratté *et al.*, 2013; Carrillo-Medina and Latorre, 2015; Carrillo-Medina and Latorre, 2016). The multiple simultaneous codes can be processed one-by-one or simultaneously to perform different tasks, and not all the readers of the signal have to be interested in the same informational aspects (Latorre *et al.*, 2006; Latorre *et al.*, 2007b; Baroni *et al.*, 2010).

In this paper, we are interested in the possible functional meaning of intraburst neural signatures. Although their role in neural computation is still unclear, previous experimental and modeling results suggest a relevant functional significance for the systems where they are present, in particular for central pattern generators (CPGs) (Brochini *et al.*, 2011; Latorre *et al.*, 2006; Rodríguez *et al.*, 2002; Latorre *et al.*, 2004; Campos *et al.*, 2007). CPGs are assemblies of neurons that, acting alone or together with other CPG circuits, produce sequential patterns of bursting activity to drive motor function (Marder and Bucher, 2001; Grillner, 2003; Selverston, 2010). We hypothesize that the ability of neural systems to "sign" their outputs and identify the origin of their inputs would have significant implications for neural sequential dynamics, leading to a more selective and complex information processing. Sequential dynamics usually underlies what is termed as rhythm or spatio-temporal pattern of activity. These are essential for the organization of complex behaviors in invertebrates as well as in vertebrates: from the alternating patterns of activity generated by CPG circuits in activities like breathing, chewing or swimming (Weimann *et al.*, 1991; Marder and Calabrese, 1996; Selverston *et al.*, 1998; Selverston, 1999; Katz, 2016); to the complex sequential dynamics in the brain for perceptive, cognitive and motor processing (Murthy and Fetz, 1996; Engel *et al.*, 2001; Buzsáki and Draguhn, 2004; Fries, 2005; Fries *et al.*, 2007; Sigman *et al.*, 2007; Duff *et al.*, 2007; Grent-'t-Jong and Woldorff, 2007; Uhlhaas *et al.*, 2010; Contreras *et al.*, 2013; Crowe *et al.*, 2014; Baertsch *et al.*, 2018). Unveiling general principles in the generation and coordination of robust sequences of neural activations is therefore a highly relevant topic in neuroscience. From this view, the departing hypothesis of this investigation was that cell-specific IBSPs may not only allow a postsynaptic cell to contextualize incoming messages and selectively react to input from specific emitters, but also to detect and discriminate specific activation sequences among different presynaptic units. Note that this requires a multiplexed encoding for information propagation regarding the "who" (neuron identity) and the "what" (sequential dynamics) of the information. In general, living cells receive many inputs from different sources. In this

scenario, if emitters encode a characteristic intraburst signature in their output, readers of these signals would receive multiple of these fingerprint simultaneously (or very close in time) through its synaptic afferents. Some specialized reader could then use incoming signatures to characterize the collective sequential activity and produce a coherent response accordingly. In particular, neural signatures would allow the reader to selectively process specific activation sequences as a function of the neurons participating in the sequence and the phase relationship among their burst firings.

To address our hypothesis, we used a detailed biophysical neuron model with a rich spiking-bursting behavior and study its response to the reception of sequences of signed bursts from different emitters. We consider that this reader cell is able to detect and discriminate specific activation sequences when, independently of the slow wave frequency of the input rhythm, a selective input-output transformation arises depending (i) on the intraburst signatures encoded in incoming signals, i.e., on the participants in the rhythm, and (ii) on their relative firing timings. Our simulations suggest history-dependent information processing capabilities associated to each input channel with fine temporal sensitivity at the subcellular and synaptic level. Information processing in the reader takes place in two simultaneous dimensions. On one hand, intraburst signatures allow the postsynaptic neuron to contextualize the information received through each synaptic afferent as a function of the signal source. On the other hand, the temporal processing of the spike trains arriving through the different input channels allows building complex input-output relations depending on the relative activation timings of different groups of presynaptic cells. The existence of such discrimination mechanisms in living systems would have relevant computational implications for the neuron, since they would permit single cells to selectively react to specific activation sequences beyond simple resonant responses. This is a highly valuable feature for the control of sequential dynamics that would have significant implications for the sequence negotiation, i.e., the process of determining participants and timings in the sequential activity.

METHODS

Characterization of neural signatures

Intraburst neural signatures are characteristic IBSPs within the spiking-bursting activity produced by a neuron (Szücs *et al.*, 2003; Szücs *et al.*, 2005). Their temporal structure can be characterized by the corresponding intraburst interspike intervals (ISIi). Then, to expose the signature encoded in a bursting signal, we built raster plots representing the firing times within the sequence of bursts in the signal. Neural activity in these plots was aligned according to the first spike in the corresponding burst. This graphical representation allowed us to visually compare differences among the signature of different neurons. Additionally, to quantitatively measure how similar two signatures were, we used the following L2 norm (Latorre et al., 2006):

$$d_{S1S2} = \sqrt{\frac{1}{B_1 B_2} \sum_i^{B_1} \sum_j^{B_2} \sum_k^N (ISI_{k,i}^{S_1} - ISI_{k,j}^{S_2})^2} \qquad (1)$$

where B_1 and B_2 are the number of bursts in signals S_1 and S_2, respective ly; and being N the number of ISIs per burst. Note that this measurement required of the burst of both signals to

have the same number of spikes.

Models. All equations of our models were numerically solved with a Runge-Kutta6(5) variable step method with a maximum error of 10^{-15}.

Neuron Model. Different neuron models, such as the models proposed by Hindmarsh and Rose (Hindmarsh *et al.*, 1984), Komendantov and Kononenko (Komendantov and Kononenko, 1996) or Liu *et al.* (Liu *et al.*, 1998), have a demonstrated ability to generate and recognize intraburst neural signatures (Latorre *et al.*, 2006; Latorre *et al.*, 2007b; Latorre *et al.*, 2004; Latorre *et al.*, 2002). To model the individual dynamics of a reader neuron, in this work we used the Komendantov-Kononenko's proposal. This conductance-based model (proposed for snail CPG cells) includes a slow-wave generating mechanism, a spike generating mechanism, an inward calcium current, an intracellular Ca^{2+} buffer and a $[Ca^{2+}]_{in}$-inhibited calcium current. Komendantov-Kononenko model neurons exhibit the rich slow-fast dynamics observed in the spiking-bursting activity of several living neuron types, which underlies their ability to produce cooperative coordinated rhythms (Elices and Varona, 2017). The membrane potential equation is:

$$-C_m \frac{dV}{dt} = I_{N_a(TTX)} + I_{K(TEA)} + I_K + I_{N_a} + I_{N_a}(V) + I_B + I_{c_a} + I_{C_a - C_a} \quad (2)$$

The slow-wave generating mechanism is given by sodium, potassium and chemo-sensitive currents:

$$I_{N_a}(V) = g^*_{Na}(V) * \frac{1}{1 + \exp(-0.2 * (V + 45))} * \left(V - V_{N_a}\right) \quad (3)$$

$$I_{N_a} = g^*_{Na} * \left(V - V_{N_a}\right) \quad (4)$$

$$I_K = g^*_K * (V - V_K) \quad (5)$$

$$I_B = g^*_B * m_B * h_B (V - V_B) \quad (6)$$

$$\frac{dm_B}{dt} = \frac{1 / (1 + \exp(0.4 * (V + 34))) - m_B}{0.05} \quad (7)$$

$$\frac{dh_B}{dt} = \frac{1 / (1 + \exp(-0.55 * (V + 43))) - h_B}{1.5} \quad (8)$$

The spike generating mechanism is described by TTX-sensitive sodium and TEA-sensitive potassium Hodgkin-Huxley type currents:

$$I_{Na(TTX)} = g^*_{Na(TTX)} * m^3 * h * (V - V_{Na}) \quad (9)$$

$$\frac{dm}{dt} = \frac{1 / (1 + \exp(-0.4 * (V + 31))) - m}{0.0005} \quad (10)$$

$$\frac{dh}{dt} = \frac{1 / (1 + \exp(0.25 * (V + 45))) - h}{0.01} \quad (11)$$

$$I_{K(TEA)} = g^*_{K(TEA)} * n^4 * (V - V_K) \quad (12)$$

$$\frac{dn}{dt} = \frac{1 / (1 + \exp(-0.18 * (V + 25))) - n}{0.015} \quad (13)$$

The inward calcium transient voltage-dependent current is described by:

$$I_{Ca} = g^*_{Ca} * m^2_{Ca} * (V - V_{Ca}) \quad (14)$$

$$\frac{dm_{Ca}}{dt} = \frac{1 / (1 + \exp(-0.2 * V)) - m_{Ca}}{0.01} \quad (15)$$

And, finally, the calcium stationary $[Ca^{2+}]_{in}$-inhibited current is given by:

$$I_{Ca-Ca} = g^*_{Ca-Ca} * \frac{1}{1 + \exp(-0.06 * (V + 45))} * \frac{1}{1 + \exp\left(K_\beta * ([Ca] - \beta)\right)} * (V - V_{Ca}) \quad (16)$$

$$\frac{d[Ca]}{dt} = p * \left(\frac{-I_{Ca}}{2Fv} - k_s * [Ca]\right) \quad (17)$$

where $\upsilon = 4\pi R^3/3$ is the volume of the cell; [Ca] is the intracellular Ca^{2+} concentration (mM), F is Faraday number (F = 96,485 C mol^{-1}), ks is the intracellular calcium-uptake rate constant and ρ is the endogenous calcium buffer capacity.

The Komendantov-Kononenko model is a very rich dynamical model able to display regular, irregular or chaotic regimes as a function of the particular choice for the values of its parameters. Parameters in our simulations were set for a regular bursting regime (Table 3.1). With these values, the isolated neuron showed a highly stereotyped behavior, both in the slow and fast dynamics (Fig. 3.1). This allowed us to study whether some specific external stimulation led the neuron from a very regular and precise regime to new transient regimes defining a c haracteristic input-output transformation.

V_{Na}	V_K	V_B	V_{Ca}	C_m	R	K_s	P	K_β
40 mV	-70 mV	-58 mV	150 mV	0.02 μF	0.1 mm	50 s^{-1}	0.002	15000 mM^{-1}
B	g_k	g_{Na}	g_{NaV}	g_B	g_{NaTTX}	g_{KTEA}	g_{Ca}	g_{CaCa}
0.00004 mM	0.25 μS	0.02 μS	0.105 μS	0.105 μS	400.0 μS	10.0 μS	1.5 μS	0.02 μS

Table 3.1 Parameters of the Komendantov-Kononenko neuron model for the regular bursting regime used in our simulations.

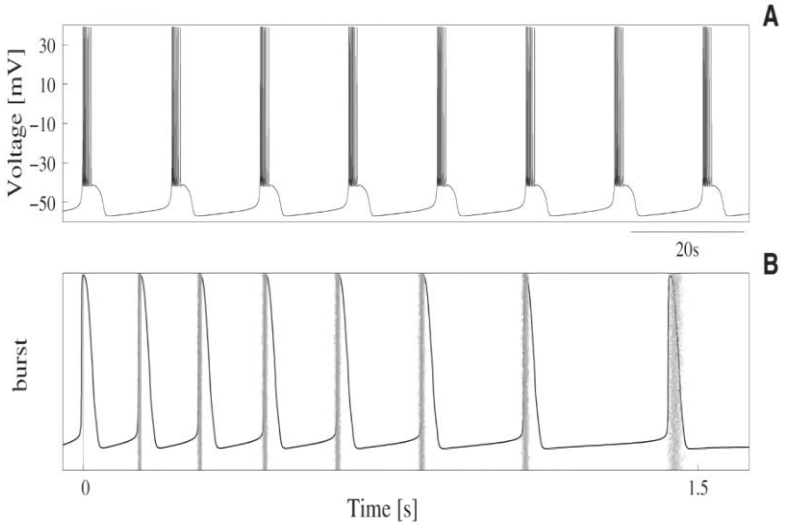

Figure 3.1 Neuron isolated dynamics. (A) Regular bursting activity of a single Komendantov-Kononenko model neuron with the parameters specified in Table 3.1. With these parameters, and in the absence of synaptic input, the reader neuron produced a highly precise sequence of decelerating 8-spike bursts at a slow-wave frequency equal to 0.13 ± 0.0007 Hz. Initial conditions are: $V_0 = -55$ mV and [Ca] = 0 mM. (B) Raster plot characterizing the IBSP of the neuron of panel A in a time series containing 5000 consecutive bursts. Action potentials are aligned (t = 0) to the first spike in the burst. Black trace corresponds to a representative burst in the series illustrating precision of the isolated neuron's fast dynamics.

Synaptic Model. To describe the synaptic input arriving at a neuron, we used the kinetic formalism for modeling chemical-mediated synaptic transmission proposed by Destexhe *et al.* (Destexhe *et al.*, 1994a; Destexhe *et al.*, 1994b). Such framework has a demonstrated ability to capture the physiological properties of biological synapses mediated by different receptor types. In our simulations, we chose parameters to represent excitatory and inhibitory connections as AMPA- and $GABA_A$-mediated synapses, respectively. Kinetics of both receptor types was simulated according to a two-state kinetic scheme (Destexhe *et al.*, 1994b). Thus, synaptic input in the reader cell was represented as an additional current in the neuron model as:

$$I_{syn}(t,V) = \sum_i r_i \, g_{syn_i}\left(V - E_{syn}\right) \tag{18}$$

where i represents the emitter neurons, g_{syni} is the maximal conductance of each connection; V is the postsynaptic potential (i.e., the membrane potential of the reader neuron); E_{syn} is the synaptic reversal potential; and the value of r_i gives the fraction of bound receptors and it is given by:

$$\frac{dr_i}{dt} = \alpha_{syn}[T](1-r) - \beta_{syn}\, r \tag{19}$$

being [T] the neurotransmitter concentration in the synaptic cleft; and α_{syn} and β_{syn} the forward and backward rate constants for transmitter binding, respectively. To compute the value of r, we assumed that [T] occurs as a spike-driven pulse initiated at the maximum voltage peak in the corresponding presynaptic unit and during which [T] = 1 mM. After that [T] = 0 mM.

Stimulation. In a general scenario, neurons can receive thousands of inputs from multiple emitters. In our experiments, we considered the minimal setting illustrated in Fig. 3.2A oriented to investigate the arising of specific input-output relations from the simultaneous processing of signals from five emitters with a characteristic intraburst neural signature. The setup consisted of a reader cell connected to a group of emitter neurons (N_i) that cooperatively produced coordinated sequential bursting activity. While the IBSP of all the bursts produced by a given emitter was always the same and different of the IBSP of the rest of emitters, i.e., the emitter cells had a characteristic intraburst signature (S_i); the frequency, participants and phase relationships of the collective rhythm they generated at a given moment might change.

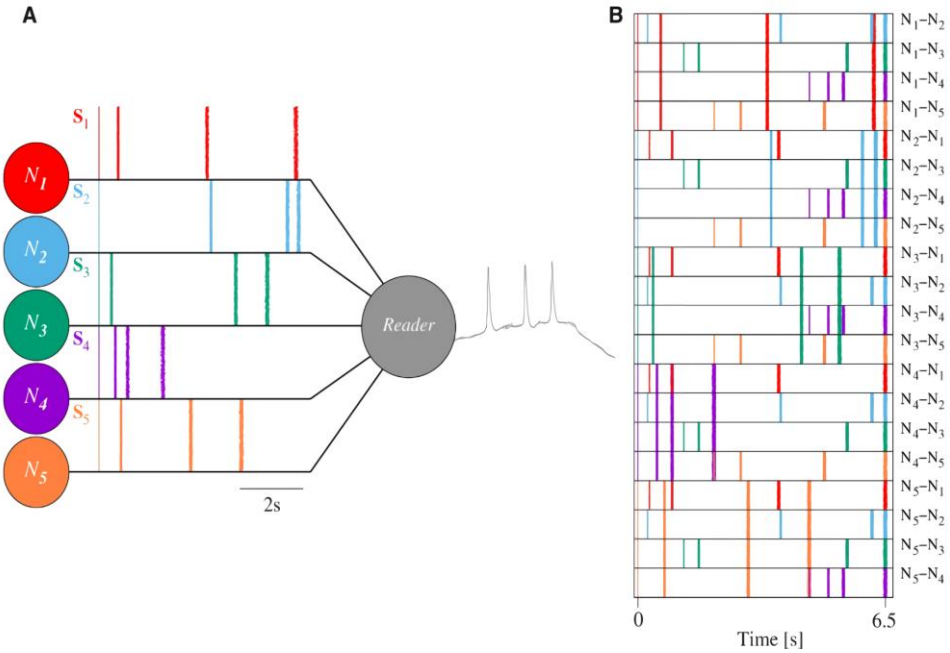

Figure 3.2 Schematic representation of the experimental setup. (A) $N_{1–5}$ were bursting neurons acting cooperatively to produce sequential patterns of spiking-bursting activity. When they fired, they generated 4-spike bursts with a characteristic intraburst neural signature (S_i). Raster plots characterizing signatures S_i contain 5000 bursts from the corresponding emitter. This graphical representation allows visually comparing the temporal structure of the five intraburst fingerprints (see also Table 3.2). The activity of neurons $N_{1–5}$ was the input of the reader neuron, that computed an output in response to the presynaptic activation sequence. (B) 2-emitter activation sequences analyzed in our simulations (N_i – N_j). Raster plots characterizing the spike timings in each sequence contain 3000 spike sequences aligned ($t = 0$) to the first spike in the sequence. The color code is the same as in panel A and identifies the spike source.

Using this simple experimental setup, we analyzed the reader's response to different precise periodic inputs delivered in the context of the global sequential dynamics produced by neurons N_i. The goal was to find preferred input-output relations in the form of stereotyped responses to specific activation sequences. Activation sequences differed in their spike timings and the input channel through which action potentials were delivered depending on the emitters that participated in the rhythm. For simplicity, the focus of our analysis was the input-output transformation during the processing of sequential patterns of activity in which the reader received coordinated input from two emitters, N_i and N_j. The corresponding 2-emitter activation sequences were characterized by the combination of the emitters' signatures, $S_i + S_j$ (Fig. 3.2B). As the reader response could strongly depend on multiple features of the incoming

spike sequences, to make our discussion more restrictive and isolate the effect of intraburst neural signatures from the information encoded in other aspects of the spiking-bursting input signals, we imposed every stimulation period to have the same duration and contained the same number of spikes.

RESULTS

As we were interested in the detection and distinct processing of combinations of intraburst neural signatures without any specific tuning in the synaptic connections, we analyzed and compared results of simulations performed with the same parameters for all the input channels of the reader neuron. In this paper, we focus on results corresponding to input patterns received through excitatory AMPA connections with g_{syni}=0.1μS, $E_{syn} = 0$ mV, $\alpha_{syn} = 0.5$ ms^{-1} mM^{-1} and $\beta_{syn} = 0.1$ ms^{-1}. Equivalent results to the ones presented here were obtained with $GABA_A$-mediated inhibitory synapses ($E_{syn} = -78$ mV).

As expected, when the reader cell was stimulated with a rhythmic input pattern of activity its behavior changed. Synaptic input elicited transient behavioral changes during the stimulation and a brief subsequent period (see panels A and B in Fig. 3.3). Taking into account that results presented in the following sections correspond to input received through excitatory synapses, note the increasing activity during the stimulation. When the stimulation was over, the neuron recovered back to the precise spiking-bursting behavior imposed by the cell intrinsic dynamics. These observations pointed to the correlation among the output spiking activity during the stimulation and the events in the input, since synaptic currents from the emitters were obviously the origin for the different behaviors displayed by the reader. In the following sections, we study whether specific combinations of neural signatures might elicit the generation of transient stereotyped responses underlying a characteristic input-output transformation in the cell.

Stimulation without neural signatures

We first studied the response of the reader neuron to the reception of coordinated bursting signals that did not encode an intraburst neural signature. For that, we performed simulations where two presynaptic cells generated rhythmic patterns of bursting activity at different slow-wave frequencies. As they had not a characteristic fingerprint, their intraburst firing pattern varied randomly within each burst. The goal was to verify whether two neurons generating a precise bursting rhythm with a random IBSP – but equivalent regarding number of spikes and duration of the stimulation in each cycle – could lead to specific input-output relations in the reader.

Unlike the precise spiking-bursting activity generated by the isolated neuron (cf. Fig. 3.1), when this was stimulated with rhythmic bursting signals not encoding an intraburst signature, its response varied and became non-predictable. This occurred regardless the number of spikes in the input sequence, the time window between first and last spike, and the frequency of the presynaptic rhythm. Panels A and B in Fig. 3.3 illustrate this result displaying two representative examples of postsynaptic output when the reader processed sequences of 4-spike random bursts from two emitters producing a rhythmic pattern of activity at different frequencies. To generate these plots and allow comparison with results presented in the

following sections, we took a special care to use a stimulation protocol equivalent to the one used below to discuss the processing of signals that encode a neural signature. In this way, we assured (i) that the reader received two 4-spike bursts through two different synaptic afferents within each rhythm cycle, and (ii) that the time interval between first and last spike in the input sequence was 6.5 seconds (see below). Given the bursting nature of the reader cell, a relevant feature pointing out the unpredictable input-output transformation during random stimulation was how postsynaptic spikes were grouped into bursts with different properties in each stimulation cycle. Panel C of Fig. 3.3 displays examples of time series showing the different organization of the output bursts in response to two 4-spike input bursts with random IBSPs, while panels D and E in this figure illustrate dispersion of the output raster plots and PSTHs during random stimulation.

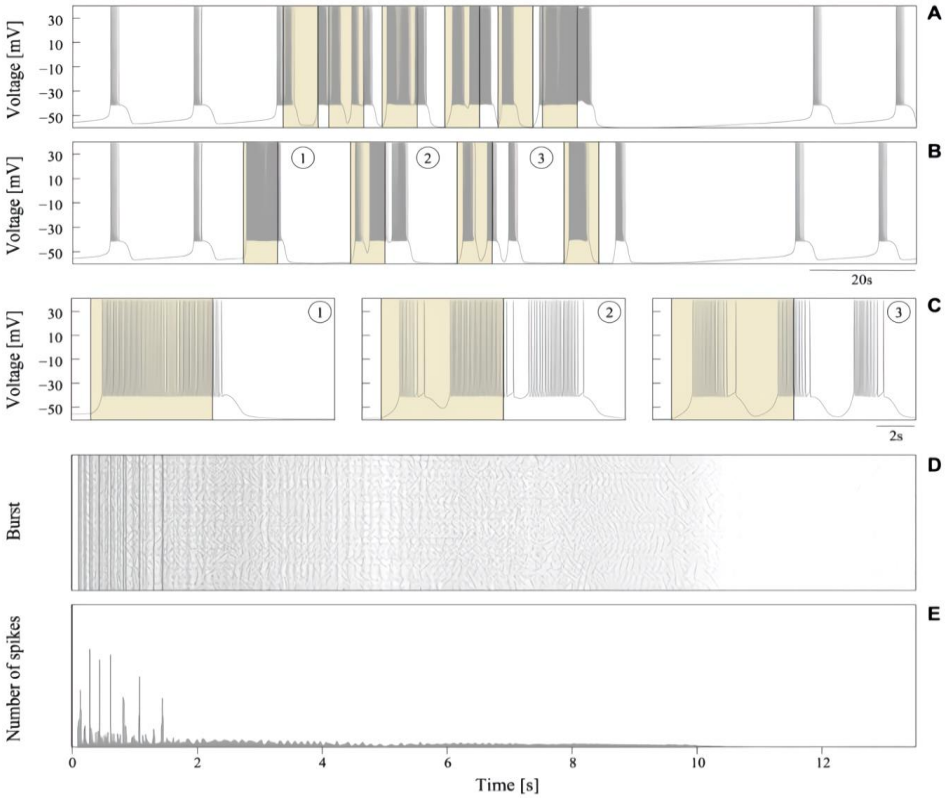

Figure 3.3 Response of the reader neuron to pairs of coordinated bursts with a random distribution of spikes. (A, B) Reader activity in response to a fast presynaptic rhythm (panel (A)) and a rhythm coherent with the slow-wave frequency of the reader (panel (B)). Shadowed areas identify the stimulation periods, defined as the time interval between the arrival of the first and the last spike in a spike input sequence (6.5 s in all cases, see main text for details). (C) Fragments of time series illustrating the different response of the reader neuron to the processing of two coordinated random bursts. Each trace corresponds to a stimulation cycle in panel (B). (D, E) Spike raster plot and PSTH characterizing the reader activity during 5000 consecutive random stimulation cycles. Spiking activity in these plots was aligned (t = 0) to the first postsynaptic spike fired after the stimulation.

The unpredictable response observed in the simulations with random bursts did not necessarily imply that the number of spikes and the duration of the stimulation in each cycle were not relevant informational aspects for the reader. The frequency of the presynaptic rhythm was an additional aspect to take into consideration in this regard, since the reader' oscillation phase at the moment the input sequence was delivered could significantly vary

depending on it (cf. panels A and B in Fig. 3.3). This variation in the phase might also be a plausible explanation for the unpredictable response in each stimulation cycle. To assess dependence of the output on the relationship between the sequence onset and the phase of the reader neuron, we performed new simulations where, departing from the same initial conditions, sequences of two bursts with random IBSPs and the same number of spikes and duration were delivered at a given fixed moment. We simulated the processing of multiple combinations of random sequences arriving at different phases of the reader oscillation. Regardless whether sequences arrived while the reader was firing or within the resting period between two consecutive bursts, the response was not predictable. Therefore, we concluded that neither the number of spikes in incoming bursts nor the time window between first and last spike in the sequence were key informational aspects for our reader cell to compute a selective response.

Detection of activation sequences by means of neural signatures

The next step in our investigation was to study the emergence of preferred neuronal input-output relations in response to sequential bursting activity encoding an intraburst fingerprint. We focused on the processing of sequences containing the same number of spikes and with the same duration. In this way, we isolated the effect of neural signatures in the input-output transformation from the effect of these additional informational aspects in the bursting activity.

The first result derived from simulations where the emitters had a characteristic neural signature was a strong dependence of the reader's output on the slow-wave frequency of the presynaptic rhythm. In our analysis, we distinguished three situations as a function of the relationship between this frequency and the reader slow dynamics. With fast rhythms (as compared with the reader's activity), input sequences usually arrived while the reader was firing a burst because of the processing of a previous input. In this situation, the same as in the case of input signals with random IBSPs (Fig. 3.3A), the reader produced unpredictable responses. This result highlighted again relevance to compute the response of the reader phase at the moment the sequence was delivered. For slow rhythms, the situation was similar in the sense that some sequences arrived while the reader was firing, in this case because of its intrinsic dynamics. Responses to these sequences were not predictable either. In terms of this work, these results implied that the reader did not implement any preferred input-output r elation for presynaptic rhythms non-coherent with its slow dynamics (i.e., much faster or slower rhythms). However, the most relevant situation from the perspective of our investigation was the processing of rhythms coherent with the reader's activity. First, because this is the most typical situation in the context of the circuits where intraburst neural signatures are present (e.g., CPG circuits). Second, because these rhythms minimized the effect of the interplay between the reader phase and the sequence onset on the postsynaptic response. As the frequency of the presynaptic rhythm became closer to the reader's oscillation frequency, as opposed to what happened with faster rhythms, the reader was able to reach the resting period before the arrival of new inputs (e.g., see Fig. 3.3B). And, as opposed to what happened with slower rhythms, sequences in the series – maybe except the first one – were always delivered within the resting period between bursts. In this situation, some specific combinations of intraburst neural signatures elicited a highly stereotyped and characteristic output in the reader. In this regard, it is important to highlight that not all the intraburst ISI

distributions allowed a selective input-output transformation.

As representative example of the emergence of preferred input-output relations in response to sequential bursting activity encoding an intraburst fingerprint, we analyze and discuss here simulations with five emitter neurons (N_1–N_5) producing bursts with four spikes (half than the bursts produced by the isolated neuron, Fig. 3.1B). The signature (S_i) of each emitter (N_i) was given by the following intraburst ISI distribution (units are seconds):

- $S_1 = \{ISI_1 = 0.60 \pm 0.02, ISI_2 = 2.80 \pm 0.02, ISI_3 = 2.80 \pm 0.02\}$
- $S_2 = \{ISI_1 = 3.50 \pm 0.02, ISI_2 = 2.40 \pm 0.02, ISI_3 = 0.35 \pm 0.02\}$
- $S_3 = \{ISI_1 = 0.40 \pm 0.02, ISI_2 = 3.90 \pm 0.02, ISI_3 = 1.00 \pm 0.02\}$
- $S_4 = \{ISI_1 = 0.50 \pm 0.02, ISI_2 = 0.40 \pm 0.02, ISI_3 = 1.10 \pm 0.02\}$
- $S_5 = \{ISI_1 = 0.70 \pm 0.02, ISI_2 = 2.20 \pm 0.02, ISI_3 = 1.60 \pm 0.02\}$

Note that a small dispersion was introduced in the ISI distributions to produce a realistic temporal variation in the intraburst spiking activity (Szücs et al., 2003; Elson *et al.*, 1999; Lago-Fernández *et al.*, 2009; Marin *et al.*, 2014). Figure 3.2A represents these five signatures as raster plots aligned to the first spike in the burst, and Table

	S_1	**S_2**	**S_3**	**S_4**	**S_5**
S_1	$8.02 * 10^{-4}$	-	-	-	-
S_2	14.6	$8.04 * 10^{-4}$	-	-	-
S_3	4.49	12.3	$8.05 * 10^{-4}$	-	-
S_4	8.66	13.6	12.3	$7.95 * 10^{-4}$	-
S_5	1.81	9.44	3.34	3.53	$8.04 * 10^{-4}$

These metrics were calculated comparing time series with 5000 bursts each. The distance of each signature to itself is shown to give a reference value for the similitude measurement.

Table 3.2 Quantifies the distance dSi,Sj (Eq. 1) between signals from each possible pair of emitter cells.

When the reader processed rhythmic patterns of bursting activity generated by two of the neurons $N_{1–5}$, it synchronized with the emitters. This was in line with the classical view on bursting activity, pointing out that the slow depolarizing bursting period was relevant to compute the reader's output. However, these rhythms also led to preferred input-output relations as a function of the source of the signals building up the coordinated pattern activity. This selective input-output transformation was independent of the presynaptic slow-wave frequency and the reader phase when the sequence arrived. Figure 3.4 shows examples of the selective response to distinct biphasic rhythms produced by neurons $N_{1–5}$. In particular, raster plots (left panels) and PSTHs (right panels) in this figure characterize the corresponding output spike timings. Note that the sequences processed in simulations of Fig. 3.4 were equivalent regarding number of spikes (n = 8), duration of the stimulation (6.5 s) and slow-wave frequency

to those shown in Fig. 3.3B–E. The only difference was the encoding of an intraburst signature which underlay the precise presynaptic IBSPs. The temporal structure of the spikes produced in the output significantly varied depending on the emitters participating in the input rhythm: from sequences of nearly regular bursts to sequences of accelerating or decelerating bursts. There were also differences regarding number of spikes, duration, phase and/or number of response bursts. Figure 3.5 quantifies these differences for all the possible biphasic rhythms produced by neurons N_{1-5}.

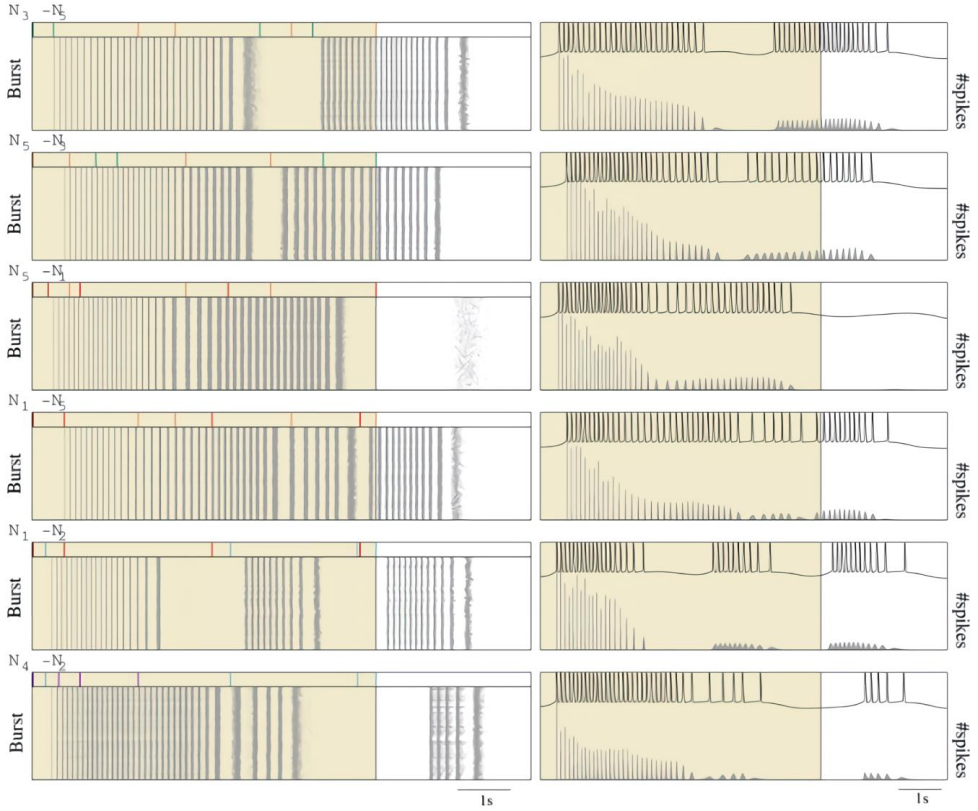

Figure 3.4. Stereotyped response of the reader to different 2-emitter activation sequences from N_{1-5}. Spike raster plots (left) and PSTHs (right) were generated considering 5000 consecutive stimulation periods – defined as the time interval between the arrival of the first and the last spike in an input sequence (shadowed areas). Postsynaptic activity was aligned to the first spike produced during the stimulation. In contrast to previous figures, the delay from delivery of the first spike in the input to the generation of the first spike in the output is now included both in the raster plots and the PSTHs. Panels on top of the raster plots display the input spike sequence in each rhythm. The color code used to identify the spike source is the same used in Fig. 3.2A. Note the precise output as compared to the random stimulation (cf. Fig. 3.3), and the characteristic stereotyped response for each pair of signals. Time series above PSTHs show an example of these characteristic responses.

Since all the properties of the presynaptic rhythms but the signatures identifying the origin of the input signals were the same, we might assume that the emerging preferred input-output relations appeared due to the presence of these precise temporal structures. However, the selective respond of the reader did not depend on the encoding of a given signature in the input, i.e., there was not a correlation between the generation of a given stereotyped output and the activation of a specific emitter. For instance, in four of the examples shown in Fig. 3.4 (see also Fig. 3.5), the reader received input from N_5 and, therefore, processed signature S_5. In all these cases, the neuron response varied – from the generation of two bursts to the

generation of a single longer or a single shorter burst – as a function of the signature encoded in the additional signal received during the stimulation cycle. This pointed to the combination of incoming signatures as responsible for the selective input-output transformation. Additionally, the order of presentation of these signatures was also relevant for determining the stereotyped response produced by the reader. Response to $S_i + S_j$ was different to response to $S_j + S_i$ (cf. responses to $N_3 - N_5$ and $N_5 - N_3$, or to $N_5 - N_1$ and $N_1 - N_5$ in Fig. 3.4). This was highly relevant for the characteristic input-output transformation discussed in this paper, since the relative arrival timing of the bursts encoding the neural signatures determined the precise activation sequence among the emitters (N_i followed to N_j or viceversa).

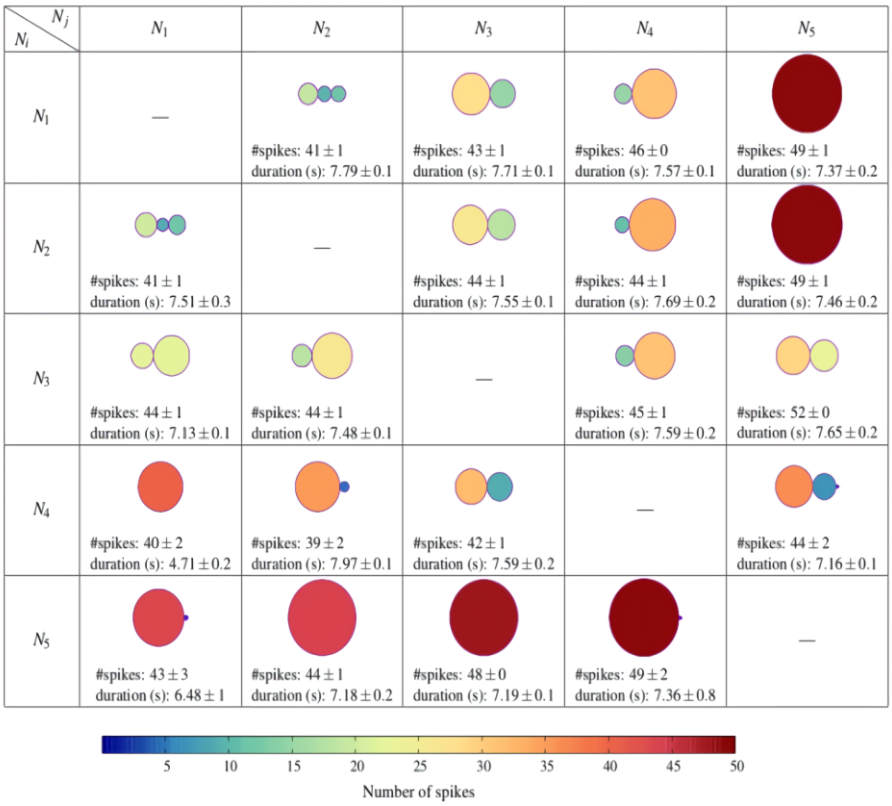

Figure 3.5 Characterization of the reader output as a function of the emitters participating in the input rhythm, i.e., of the combination of signatures processed by the neuron in a stimulation cycle. Circles represent series of bursts produced in the output in response to a given input sequence ($N_i - N_j$): from 1 to 3 response bursts depending on the input. The size and the color of the circles (see color-map at the bottom) represent the mean duration and the mean number of spikes in the corresponding output burst, respectively. Note that this representation does not allow the comparison of the intraburst temporal structure of the bursts. For this, we use the output raster plots and PSTHs. Data included in each cell correspond to the mean number of bursts produced in response to the corresponding activation sequence, the mean total number of spikes and the mean total duration of the response – computed as the time interval between the first and the last output spike produced in response to the input sequence.

Results confirming the selective input-output transformation as a function of the identification of activation sequences by means of the recognition of intraburst signatures were observed in simulations (i) where the bursting activity of the second active emitter was slightly anticipated or delayed (Fig. 3.6), or (ii) where a combination of presynaptic signals defined an input spike pattern equivalent to $S_i + S_j$ but with some spike delivered through a different synapse (e.g., eight single spikes delivered through eight different input channels or 8-spike

bursts arriving through a single channel, Fig. 3.7). If we compared the reader's response in these simulations with the corresponding stereotyped response produced when processing $S_i + S_j$, the output changed and even became unpredictable. These simulations also served to illustrate the underlying mechanisms behind the recognition of specific combinations of intraburst signatures. With this aim, Figs 3.6 and 3.7 display the trajectories of the synaptic variables within a stimulation cycle. The analysis of these trajectories revealed relevance to compute the output of the interplay among the multiple time scales involved in the synaptic processes, the intrinsic dynamics of the reader neuron and the temporal structure of the inputs. These complex interactions could give rise to highly different input-output transformations with only a small variation in the input spike timings (e.g., compare top and bottom panel in Fig. 3.6). Even in the case of action potentials arriving at the same relative timing but delivered through different afferents, the interplay among these temporal dynamics played a critical role in the computation of the output. In particular, synaptic temporal dynamics induced significant changes in the evolution of the total fraction of bound receptors during the stimulation depending on the stimulation history of the synaptic afferent. This underlay the non-linear sum of synaptic currents responsible of producing different responses in each case (cf. gray and black traces in Fig. 3.7). These results reflected the complex interaction among the resonant processes involved in the computation of the model neuron response, suggesting that intraburst neural signatures, whose constituent spikes must be delivered through the same input channel, could not only allow a postsynaptic neuron to react selectively to specific activation sequences among its presynaptic partners, but also to precise phase relationships among the active cells.

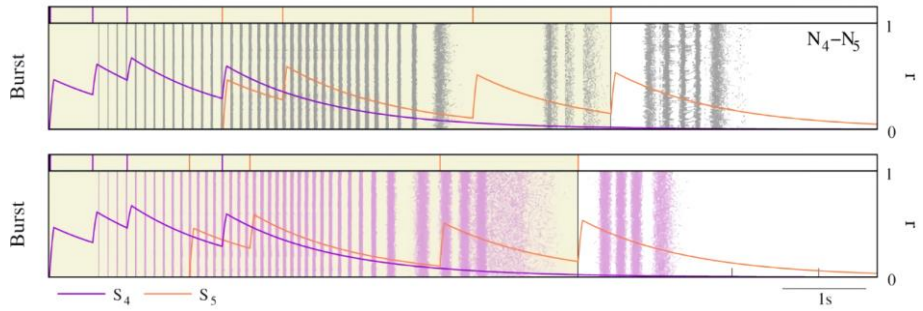

Figure 3.6 Response of the reader to a temporal shift in the activation sequence. Raster plots equivalent to the ones shown in Fig. 3.4 illustrating the different response of the reader to the activation sequence $N_4 - N_5$ (top) when the activity of N_5 was slightly anticipated in relative to bursts from N_4 (bottom). Purple and orange traces show temporal evolution of the variable r corresponding to the connection between the reader and neurons N_4 and N_5, respectively.

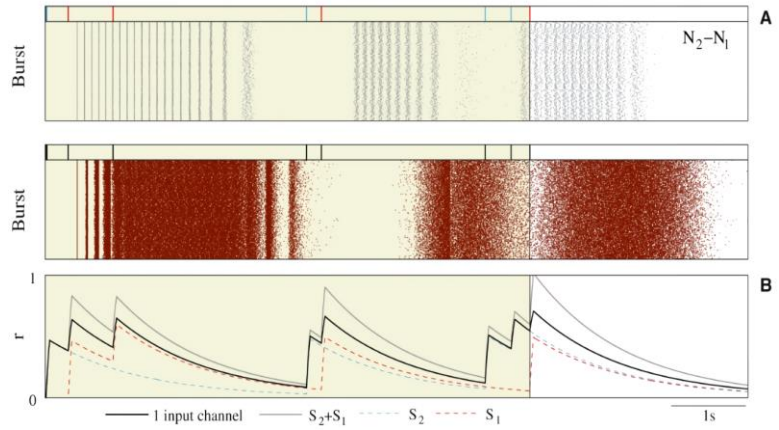

Figure 3.7 Comparison of the reader response to two intraburst signatures and to a single burst with an equivalent IBSP. (A) Output raster plots equivalent to the ones shown in previous figures, in this case characterizing the stereotyped response produced when the reader processed the activation sequence $N_2 - N_1$ (top) and the non-predictable response to sequences of 8-spike bursts from a single presynaptic unit with an IBSP equivalent to $S_2 + S_1$ (bottom). (B) Trajectories of the corresponding synaptic variables r in response to a representative input spike pattern in each case. Gray trace corresponds to the combined action of signatures S_2 and S_1 in the synaptic cleft. Action potentials from N_1 (cyan) and N_2 (red) were delivered through a different synaptic channel (dotted traces). Black trace corresponds to the single emitter case.

Finally, to assess robustness of the detection of activation sequences, we introduced in Eq. 2 additive white noise computed from a uniform distribution on the interval [0, max_{noise}] at each time step, and performed simulations with different levels of noise as indicated by the value of max_{noise}. All discussed phenomena occurred both in the presence and absence of noise, even for levels of noise affecting the precise slow and fast dynamics of the isolated neuron (Fig. 3.8) or leading it to a chaotic spiking regime. Simulations with a maximum noise level below 30% of the maximal synaptic current received by the reader produced the same results of the simulations presented in this paper. For higher levels (up to 43% of the maximum synaptic current), stereotyped responses to each combination of signatures could change, but results were equivalent. Results of these simulations pointed out the robustness of the discussed phenomena.

Figure 3.8 Robustness to noise of the discussed phenomena. (A) Response of the reader to the processing of the activation sequence $N_5 - N_4$ in a simulation without noise. (B) Response to the same activation sequence in a simulation with a maximum noise amplitude equal to 0.44 (around 20% of the maximal synaptic current received by the reader). Note that although noise affected the frequency and IBSP of the reader in the absence of stimulation (first part of time series), it produced the same stereotyped response to $S_5 + S_4$.

DISCUSSION

Neural signatures are robust and cell-specific intraburst firing patterns that can be found in different bursting neurons (Szücs *et al.*, 2003; Szücs *et al.*, 2005; Garcia et al., 2005; Zeck and Masland, 2007; Brochini *et al.*, 2011). Although the existence of these fingerprints does not guarantee that nervous systems make use of such temporally precise code, information processing based on their identification can be a powerful strategy for neural systems to enhance their capacity and performance. In this paper, we have studied these neuron-specific temporal structures from a functional point of view. We show that a neuron conductance-based model is able to take advantage of them to identify the origin of its input signals and sensitively adjust its response to specific activation sequences. The response of our reader cell varies as a function of different features of the input, in particular, as a function of the frequency of the presynaptic rhythm, the number of spikes in incoming bursts and the duration of the stimulation. In our study, we take a special care to isolate the effect of intraburst neural signatures from these additional informational aspects of the spiking-bursting signals. The reader response has anyway a strong dependence on the slow-wave frequency of the presynaptic activity. Depending on this frequency, the oscillation phase of the reader at the moment the input sequence arrives is one of the main factors determining the output. Nevertheless, for presynaptic rhythms coherent with the reader activity, if the signals that constitute the input sequential pattern encode a characteristic signature identifying their source, the output does not depend on the reader's oscillation phase. In this situation, specific combinations of intraburst fingerprints lead to complex preferred input-output relations, and the reader produces characteristic stereotyped bursting responses depending on the cells participating in the rhythm and the precise phase relationship among their bursting activity. Changes in the firing order of the emitters, in their IBSPs, in their timings within the sequence or in the synaptic afferent through which action potentials are delivered induce changes in the output. The emergence of such preferred input-output relations supports the hypothesis of the recognition of specific activation sequences by means of the emitters' characteristic intraburst signature. Besides this, the reader synchronizes in any case with the presynaptic rhythm, which highlights that it uses the information encoded in different aspects of the input signals to compute its output.

Relevance of detecting activation sequences becomes apparent when we consider neurons at the population level. When a group of neurons working together to perform a given task produces precise and reliable spike trains, the neurons they are connected with receive sequential trains of spikes from different sources (Shlens *et al.*, 2006; Quian Quiroga and Panzeri, 2009; Wang, 2010; Danner *et al.*, 2015). Robust sequences of neural activations have been described in many invertebrate and vertebrate systems((Weimann *et al.*, 1991; Marder and Calabrese, 1996; Selverston *et al.*, 1998; Selverston, 1999; Katz, 2016; Murthy and Fetz, 1996; Engel *et al.*, 2001; Buzsáki and Draguhn, 2004; Fries, 2005; Fries *et al.*, 2007; Sigman *et al.*, 2007; Duff *et al.*, 2007; Grent-'t-Jong and Woldorff, 2007; Uhlhaas *et al.*, 2010; Contreras *et al.*, 2013; Crowe *et al.*, 2014; Baertsch *et al.*, 2018). These sequences play a critical role to

encode, control and execute information in different sensory, central and motor networks (Rabinovich *et al.*, 2008; Kiebel *et al.*, 2009; Fiete *et al.*, 2010; Latorre *et al.*, 2013; Fingelkurts and Fingelkurts, 2017). In this scenario, the preferred input-output relations discussed in this paper would allow some specialized readers to build context dependent responses as a function of certain relevant activation sequences, while other readers keep blind to intraburst signatures and completely ignore these temporal structures in their input signals. This selective input-output transformation can result in information discrimination mechanisms associated to the generation and coordination of sequential dynamics. For example, even the rhythms generated by simple CPG circuits are highly flexible (Selverston and Moulins, 1987; Harris-Warrick, 2011). On one hand, the shape and phase relationships of the electrical activity of CPG neurons are continuously adapted to an everchanging environment (Selverston, 2010; Combes *et al.*, 1999; Serrano, 2007; Briggman and Kristan, 2008; McCrea and Rybak, 2008; Blitz and Nusbaum, 2011). On the other hand, many CPGs are multifunctional networks capable of switching between more than one behavior depending on the particular circumstances under which the circuit is working (Latorre *et al.*, 2013; Norekian and Satterlie, 1996; Jing and Weiss, 2001; Stein, 2004; Berkowitz *et al.*, 2010). Behavioral changes of a CPG are related, for instance, to variations of the slow depolarizing frequency, of the firing timings among the interacting elements or of the participants in the sequential pattern of activity. The properties of the rhythm generated by the network at a given moment arise from the combination of the intrinsic properties of each individual cell, the connection topology of the network, the properties of the synaptic connections and the modulatory inputs (Selverston, 1998; Flamm and Harris-Warrick, 1986; Johnson and Harris-Warrick, 1997; Kloppenburg *et al.*, 1999; Peck *et al.*, 2001; Gjorgjieva *et al.*, 2016). Our results suggest that the ability of single CPG neurons to discriminate different activation sequences could be an additional factor contributing to shape the resultant pattern during the rhythm negotiation. Additionally, external readers of an ongoing CPG rhythm could identify changes in the activation sequence of the interacting neurons, and consequently adapt their behavior to these changes.

A relevant question regarding the emergence of the preferred input-output relations discussed in this paper is what mechanisms could underlie the detection and discrimination of different activation sequences by means of the emitters' intraburst neural signature. There is not a simple answer to this question. The recognition of intraburst fingerprints requires of history-dependent processing capabilities in the postsynaptic cell. History-dependent processing capabilities offered by intrinsic neural dynamics have long been investigated and, currently, it is well-known that neurons can carry information about its history of stimulation through its dynamical variables. In particular, certain ionic currents have been considered as molecular basis for single-cell transient memory due to the history dependence on the dynamics of the corresponding ionic channels (Turrigiano *et al.*, 1996; Marder *et al.*, 1996; Egorov *et al.*, 2002; Winograd *et al.*, 2008). Previous computational studies with Hodgkin-Huxley type models (Latorre *et al.*, 2006) suggest that this could be the single-neuron substrate of history-dependent processing for the recognition of neural signatures in CPG cells. In particular, kinetics of the calcium-dependent channels affects the response to a signal encoding a particular signature. However, our work here hints at the synaptic dynamics as an additional factor to take into consideration. Our results suggest that the recognition of different sequences depends on the complex interaction among the multiple time scales involved in the processing of incoming signals through the different input channels and the reader intrinsic dynamics, which reshapes the resonant properties of the neuron. However, additional biophysical

mechanisms proposed in literature as candidates for decoding precise temporal codes at the single-cell level (e.g, see refs: Chabrol *et al.*, 2015; Latorre *et al.*, 2016; Izhikevich *et al.*, 2003; Thomson and Deuchars, 1994; Abbott, 1997; Kavalali, 2007; Cardin *et al.*, 2010; Panzeri *et al.*, 2014) could also apply for the recognition of neural signatures and activation sequences in living cells.

Finally, we would like to highlight that, although we have mainly related our work to CPG sequential dynamics, our results are not limited to these networks. As we have previously pointed out, sequential dynamics can be found in almost any vertebrate system linked to complex behaviors. Even most brain rhythms, typically characterized by their frequency, are built from sequential activations of different groups of neurons (Buzsaki, 2006; Ma and Zhang, 2018). Precise timings in the spiking activity of multiple neurons have also been reported in widely different invertebrate and vertebrate neural systems (e.g., see refs: Reinagel and Reid; 2000; Chi and Margoliash, 2001; Mao *et al.*, 2001; Reinagel and Reid; 2002; Hunter and Milton, 2003; Luczak *et al.*, 2006; Benedetti *et al.*, 2009). Furthermore, CPGs are valuable biological models for investigating and understanding neural dynamics (Katz et al., 2013). Findings on these simple neural networks have proven to be generalized to more complex networks in order to explain the computational properties of the nervous system (Selverston, 2010; Selverston, 2009, Marder and Bucher, 2007). In this line, they have been proposed as a conceptual framework for understanding cortical microcircuits (i.e., functional ensembles of neurons) because of their morphological and dynamical properties (Yuste *et al.*, 2005). In this way, coordination mechanisms based on the emission and recognition of neural signatures can arise, for instance, in the vertebrates' spinal cord, where multiple bursting neurons work together to generate rhythmic patterns of activity in a hierarchical motor network (Danner *et al.*, 2015; Gordon and Whelan, 2006; Grillner, 2006; Grillner and Jessell, 2009; Hagglund *et al.*, 2013). Therefore, we speculate that the detection of activation sequences by means of the recognition of characteristic neural signatures can have a place in the arsenal of strategies of information processing in the nervous system.

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--- SINTESIS DE RESULTADOS Y DISCUSIÓN ---

Nuestra investigación inicialmente identifica modelos computacionales para el estudio de mecanismos de codificación y procesamiento de información basados en el reconocimiento de firmas neuronales. Por un lado, extendemos el modelo desarrollado por Tristán et al. (2004), para analizar la influencia de distintas topologías de conectividad en las propiedades emergentes de la red. Por otro lado, definimos un modelo de red tipo spiking en el que se hace uso de firmas neuronales, mecanismos de plasticidad subcelular dentro de las células individuales y diferentes esquemas de codificación simultáneos para analizar las propiedades autoorganizativas de la red. Y finalmente se define un modelo realista de neurona basado en conductancia para detectar secuencias específicas de activación aprovechando la identificación de firmas neuronales intraburst. En esta sección se presenta una síntesis de los resultados obtenidos en cada uno de los trabajos de investigación compendiados en esta tesis y la discusión de los mismos.

Capítulo 1
Dinámica neuronal basadas en el reconocimiento de firmas neuronales

En la dinámica colectiva de la red propuesta, coexisten diferentes patrones espacio-temporales coherentes asociados a las firmas neuronales introducidas como estímulos externos. La capacidad de codificación y procesamiento de la red está relacionada con la competencia establecida entre la actividad espontánea y la actividad provocada por la llegada de estímulos. Dependiendo de los parámetros intra-unidad, esta competencia puede cambiar de un régimen "con ganador" (*winner-take-all*) a uno "sin ganador" (*winnerless*) (Afraimovich *et al.*, 2004; Rabinovich *et al.*, 2006) (ver Figuras 1.7 y 1.8). Cuando la competición es de tipo "con ganador", una de las firmas inyectadas prevalece sobre las otras y sólo los patrones de actividad asociados a esta firma viajan por toda la red, ya sea de forma local o global (Figura 1.9 y 1.12 paneles C y D). Por otro lado, cuando se produce una competición de tipo "sin ganador", la capacidad total de codificación/almacenamiento de la red se distribuye alternadamente entre las diferentes firmas en toda la red (Figura 1.9 y 1.12 paneles A y B). Los principales factores que conducen la competición son el nivel de actividad espontánea y la permeabilidad a los estímulos externos. Estos factores dependen de la combinación de dos parámetros intra-unidad: la probabilidad espontánea (p_e) y la probabilidad de reconocimiento (p_r), son parámetros subcelulares que controlan respectivamente el nivel de actividad espontánea y la permeabilidad de la neurona a los estímulos externos. Además, se observa que el patrón de conexión específico entre neuronas influye en la organización espacial de la dinámica colectiva de red. La presencia de conexiones aleatorias tiene un efecto similar a incrementar la permeabilidad a los estímulos externos (Tabla 1.3 y 1.4). Estas conexiones facilitan la detección de estímulos externos específicos ya que aumentan la velocidad de propagación del estímulo y el nivel de actividad asociado a él. Por el contrario, redes con conexiones más regulares promueven la competición de estímulos externos (Tabla 1.7). Esto implica que estas redes son capaces de codificar un mayor número de estímulos simultáneamente. Cuando el nivel de la actividad espontánea es demasiado alto, esta gana la

competencia, de forma que la actividad provocada por los estímulos externos desaparece casi instantáneamente de la red, lo cual evita la generación de patrones espacio-temporales asociados a estímulos externos. Esto proporciona un mecanismo de "reset", es decir, la red deja de procesar estímulos (Tabla 1.2, 1.3, 1.6).

Una vez finalizada la estimulación, surgen los mismos regímenes de competición entre los patrones espacio-temporales coexistentes provocados por los estímulos externos. La única diferencia es que, ahora, estos patrones no están sustentados por la estimulación. Cuando un estímulo pierde la competencia con otros estímulos (inclusive con la actividad espontánea) esta desaparece completamente de la red. Así, los patrones de actividad pueden desaparecer casi instantáneamente de la red, cuando termina la estimulación (Tabla 1.6). Aunque para algunas aplicaciones y sistemas de procesamiento de información ésta puede ser una propiedad deseable. Las situaciones más interesantes desde el punto de vista dinámico son aquellas en las que la red muestra capacidades de memoria a corto o largo plazo. En redes de memoria a corto plazo, la actividad inducida por el estímulo reverbera transitoriamente después de terminada la estimulación (Figura 1.10). Por el contrario, en redes de memoria a largo plazo, los estímulos conducen a la red a un nuevo estado estable y los patrones sobreviven permanentemente hasta que llega un nuevo estímulo (Figura 1.11). Dependiendo de los parámetros intra-unidad, una memoria a corto plazo puede convertirse en una memoria a largo plazo sólo incrementando la permeabilidad a los estímulos externos, y viceversa (Tabla 1.5; Figura 1.5). De igual manera, redes con conexiones más regulares benefician los mecanismos de memoria a corto plazo; mientras que redes más aleatorias potencian los mecanismos de memoria a largo plazo.

Las distintas dinámicas generadas en respuesta a los estímulos externos dependen de la combinación de los parámetros intra-unidad que afectan al procesamiento individual de la información y de la conexión entre neuronas, mismos que pueden ajustar las propiedades autoorganizativas de la red. Nuestras simulaciones con un modelo simple de red de neuronas, las cuales se comunican mediante el intercambio de firmas, muestran diferentes dinámicas complejas de red. Esto indica la gran adaptabilidad de la red a diferentes modos de funcionamiento.

Capítulo 2
Implementación de redes neuronales basadas en firmas con neuronas de tipo spiking

Desde el punto de vista dinámico se hace necesario realizar modelos más realistas para la actividad de neuronas individuales, lo que pueden introducir una mayor capacidad de procesamiento de información en la red. En el presente trabajo mostramos una red de neuronas spiking que hace uso de estrategias de multicodificación para propagar información y usa plasticidad subcelular para contextualizar o discriminar localmente los datos recibidos por una unidad. Además, cada neurona de la red tiene una firma neuronal asociada que permite su identificación inequívoca por el resto de las células. El ingreso de estímulos provoca diferentes patrones espacio-temporales que se propagan por la red aprovechando las múltiples modalidades de codificación simultánea, para transformar las entradas en diferentes espacios espacio-temporales, y organizar y coordinar los patrones de actividad transitoria coexistentes, en respuesta a un conjunto de datos. Cuando coexisten múltiples patrones en la misma dimensión surge una competencia entre ellos. Se muestran varios tipos de competencias que surgen sin conexiones inhibitorias en la red. Dependiendo

de los parámetros que conforman las reglas de plasticidad intra-unidad, al igual que en el modelo anterior, se presenta diferentes regimenes de competencia. De manera análoga, los patrones espacio-temporales producidos por los estímulos y las correspondientes dinámicas competitivas también pueden sobrevivir por largos períodos después de finalizada la estimulación. Este efecto de reverberación permite a la red memorizar/almacenar los datos de entrada, mostrando capacidades de memoria a corto o largo plazo en los diferentes espacios espacio-temporales. (Figura 2.6).

La capacidad de memoria/almacenamiento de la red, en cada dimensión varía, al ajustar los parámetros sinápticos y/o intra-unidad. Esto facilita el paralelismo y multifuncionalidad en la red. En cada una de las modalidades se pueden implementar diferentes estrategias de procesamiento intra-unidad, dependientes de la historia, para calcular la respuesta de salida de una neurona, por ejemplo, en la modalidad de codificación de firmas como una función de las señales de entrada y en la modalidad de frecuencias como una función de la frecuencia de disparo de los emisores.

Estos resultados muestran la rica dinámica y la gran flexibilidad de la red propuesta para codificar y procesar información en diferentes espacios espacio-temporales. Los mecanismos de plasticidad dentro de las células individuales y las estrategias de multicodificación pueden proporcionar propiedades computacionales adicionales a las redes neuronales spiking, lo que podría mejorar su capacidad y rendimiento. En particular, los mecanismos de contextualización local permiten a las neuronas individuales procesar múltiples códigos simultáneos en sus señales de entrada de forma selectiva o global, para determinar o ponderar completamente la decisión sobre su salida en los diferentes esquemas de codificación. Este procesamiento de información proporciona un marco para modelar procesos complejos de alta dimensión, que pueden ser aplicados a diferentes problemas computacionales del mundo real.

Capítulo 3
Mecanismos de detección de secuencias de activación en neuronas spiking-bursting por medio del reconocimiento de firmas neuronales

En este contexto, aquí mostramos que un modelo de neurona (célula lectora) basado en conductancia es capaz de reconocer secuencias de activación específicas de una combinación de emisores con una firma neuronal característica, ajustando sensiblemente su respuesta en función de cuál es el origen de las señales de entrada. En la comunicación con señales spiking-bursting, la respuesta de una célula lectora puede variar en función de diferentes características de entrada, en particular, en función de la frecuencia presináptica, del número de spikes por bursts de entrada y/o de la duración de la estimulación. Por ello, en nuestro estudio, ponemos especial cuidado en aislar el efecto de las firmas intraburst de estos aspectos adicionales de información de las señales spiking-bursting. La respuesta del lector depende en gran medida de la frecuencia de onda lenta de la actividad presináptica. Dependiendo de ésta, varía la fase de oscilación del lector en el momento que llega la secuencia de entrada (Figura 3.3). Sin embargo, para ritmos presinápticos coherentes con la actividad del lector, si las señales que conforman el patrón de entrada codifican una firma característica identificando su fuente, la salida no depende de la fase de oscilación del lector.

En esta situación, combinaciones precisas de firmas específicas en la entrada del modelo de neurona revelan relaciones preferenciales de entrada/salida complejas. La existencia de esta

relación preferencial de entrada/salida señala que la neurona es capaz de reconocer secuencias de activación específicas entre las neuronas presinápticas (Figura 3.4 y 3.5). El lector produce respuestas bursting altamente estereotipadas características que dependen de las células participantes en el ritmo y de su relación de fase precisa.

En este escenario, un punto de interés de nuestro estudio son las respuestas cuando se producen cambios en el orden de disparo de los emisores. La respuesta resulta ser distinta cuando la misma secuencia temporal de potenciales de acción se recibe por un mismo canal o por una combinación diferente de canales (Figura 3.6 y 3.7). La aparición de estas relaciones preferenciales entrada-salida apoyan la hipótesis del reconocimiento de secuencias de activación específicas por medio de firmas neuronales intraburst de los emisores. Además, el lector se sincroniza con el ritmo presináptico, destacando el uso de la información codificada en diferentes aspectos de la señal de entrada para producir su salida.

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Según el esquema de procesamiento propuesto, podría explicar por qué algunos sistemas son escasamente activos, incluso recibiendo una gran cantidad de estímulos. las neuronas sólo dispararían cuando reconocen un patrón característico en los estímulos de entrada; mientras que la señal no reconocida sería simplemente ignorada. En las simulaciones realizadas, en todos los modelos propuestos se observan dinámicas muy ricas y diversas en respuesta a estímulos introducidos en unas pocas neuronas. Las propiedades autoorganizativas de la red son complejas y altamente dependientes del patrón de conectividad entre neuronas y de los parámetros intracelular que afectan al procesamiento, contextualización y discriminación de firmas. Todas estas propiedades confieren a la red capacidades adicionales para el procesamiento de información. En particular, asumiendo i) que el sistema nervioso dispone de mecanismos de multiplexación de información en distintos aspectos de una misma señal (Friedrich et al., 2004; Gire et al., 2013; Hong et al., 2016; Kayser et al., 2009; Panzeri et al., 2010), ii) la participación de las distintas firmas neuronales reportadas en la literatura (Brochini et al., 2011; Campos et al., 2007; Szücs et al., 2003; Szücs et al., 2005; Zeck and Masland, 2007), en una estrategia multicódigo y iii) mecanismos de contextualización local de información basados en el reconocimiento de estas firmas (Latorre et al., 2006; Latorre et al., 2007), las neuronas individuales podrían procesar, de forma selectiva o global, distintas firmas simultáneas en sus señales de entrada para decidir o pesar la decisión acerca de su salida en los diferentes esquemas de codificación. Como un caso particular de un mecanismo de contextualización, una neurona podría ignorar las señales de emisores que no es capaz de reconocer y de aquellos que reconoce su firma interpretar sólo aquella información codificada en los aspectos de la señal en los que está especializada.

Los resultados obtenidos con el modelo realista de neurona apoyan la hipótesis del reconocimiento de secuencias de activación específicas a través de las firmas neuronales, características de los emisores. Lo cual proporcionaría a las neuronas individuales capacidades mejoradas para controlar y negociar la dinámica secuencial. La importancia de la detección y el control de secuencias de activación se hace evidente cuando se consideran neuronas a nivel grupal. Cuando un grupo de neuronas trabaja de manera conjunta para realizar una tarea común suelen generar trenes de spikes con cierto grado de sincronismo (Danner et al., 2015). Generar y procesar estas secuencias es esencial para producir comportamientos complejos en vertebrados e invertebrados: desde un simple patrón de actividad generado por un CPG en

actividades como la locomoción, la respiración, la masticación o la natación (Marder and Calabrese, 1996; Selverston, 1999); hasta dinámicas secuenciales complejas en el cerebro y en el procesamiento perceptivo, cognitivo y motor (Crowe *et al.*, 2014; Murthy and Fetz, 1996).

--- CONCLUSIONES ---

A continuación, se enumeran las conclusiones generales obtenidas en el trabajo de investigación desarrollado a lo largo de mi tesis doctoral:

1. En esta tesis doctoral hemos desarrollado modelos computacionales para estudiar posibles mecanismos de codificación y procesamiento de información en el sistema nervioso. Las simulaciones y resultados presentados apoyan la hipótesis de que las firmas neuronales, y en general la estructura temporal existente en la dinámica rápida de la actividad de neuronas con comportamiento en ráfagas, forman parte del arsenal de mecanismos de codificación y procesamiento temporal de información de que dispone el sistema nervioso para optimizar su proceso de comunicación.

2. Nuestros modelos de red basados en firmas neuronales proponen diferentes mecanismos de procesamiento muy simples utilizando una memoria transitoria (contexto de información local) que realiza el seguimiento de la información recibida, es decir, un mecanismo de contextualización dependiente de la historia en cada unidad neuronal. El uso de firmas neuronales para identificar el origen de los mensajes de entrada permite implementar reglas de procesamiento, que no sólo afectan a los parámetros que intervienen en la contextualización/discriminación local de información, sino que también a la conectividad. La eficiencia de la red depende de la relación de equilibrio entre el coste computacional y las ventajas que proporcionan estos tipos de mecanismos.

3. El modelo propuesto de red con neuronas spiking representa una prueba de concepto con una rica dinámica y una gran flexibilidad para codificar y procesar información mediante la generación y propagación de patrones espacio-temporales en diferentes dimensiones. Resulta ser un valioso aporte sobre el tratamiento de información en el contexto de las redes neuronales, ilustrando la riqueza dinámica que la plasticidad subcelular puede proporcionar a este tipo de redes. Esta es una capacidad muy deseable en los sistemas paralelos y multifuncionales que podrían ser aplicados para resolver diferentes tipos de problemas. Este tipo de mecanismos de codificación podría aumentar el poder computacional de las redes de tipo spiking y su capacidad para modelar procesos complejos de alta dimensión.

4. Nuestras simulaciones con un modelo de neurona basado en conductancias revelan relaciones de entrada-salida preferenciales complejas al combinar firmas específicas en su entrada. Las firmas neuronales permitirían al lector i) procesar selectivamente secuencias de activación específicas en función de las neuronas que participan en la secuencia y en la relación de fase entre sus períodos de actividad, ii) producir una respuesta coherente. En determinadas circunstancias un lector puede estar interesado en un tipo de información y en otras circunstancias estar interesado en otro. Esta capacidad de discriminar información en los lectores, en función de sus entradas, es muy deseable en múltiples sistemas de comunicación de cualquier índole.

5. En el contexto de los CPGs o sistemas biológicos equivalentes, la capacidad de discriminar

información en base a su origen podría tener importantes implicaciones para la negociación de ritmos. Los lectores externos de un ritmo en curso podrían identificar cambios en la secuencia de activación de las neuronas que interactúan y, consecuentemente, adaptar su comportamiento a estos cambios.

6. Durante más de 60 años se han utilizado paradigmas de redes neuronales artificiales con una limitada inspiración biológica. En los últimos años se han propuesto nuevos paradigmas bio-inspirados. Aún así, los mecanismos de codificación y procesamiento de información basados en la existencia de unidades distinguibles no han sido estudiados en gran detalle. Los modelos presentados en esta tesis son uno de los primeros pasos en esta línea. La identificación del origen de la señal da una mayor importancia a la individualidad de las neuronas, permitiendo un procesamiento altamente selectivo de la información al disponer de mecanismos de contextualización/discriminación local. Desde un punto de vista teórico, esto podría conducir a los sistemas neuronales a incrementar de forma muy significativa su capacidad y rendimiento. Además, en el contexto de la aplicación de las redes neuronales a la inteligencia artificial, múltiples problemas podrían verse beneficiados por el uso de estos mecanismos. Para profundizar en este estudio y su aplicabilidad, se hace necesario realizar análisis más detallados, tanto a nivel teórico como experimental.

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